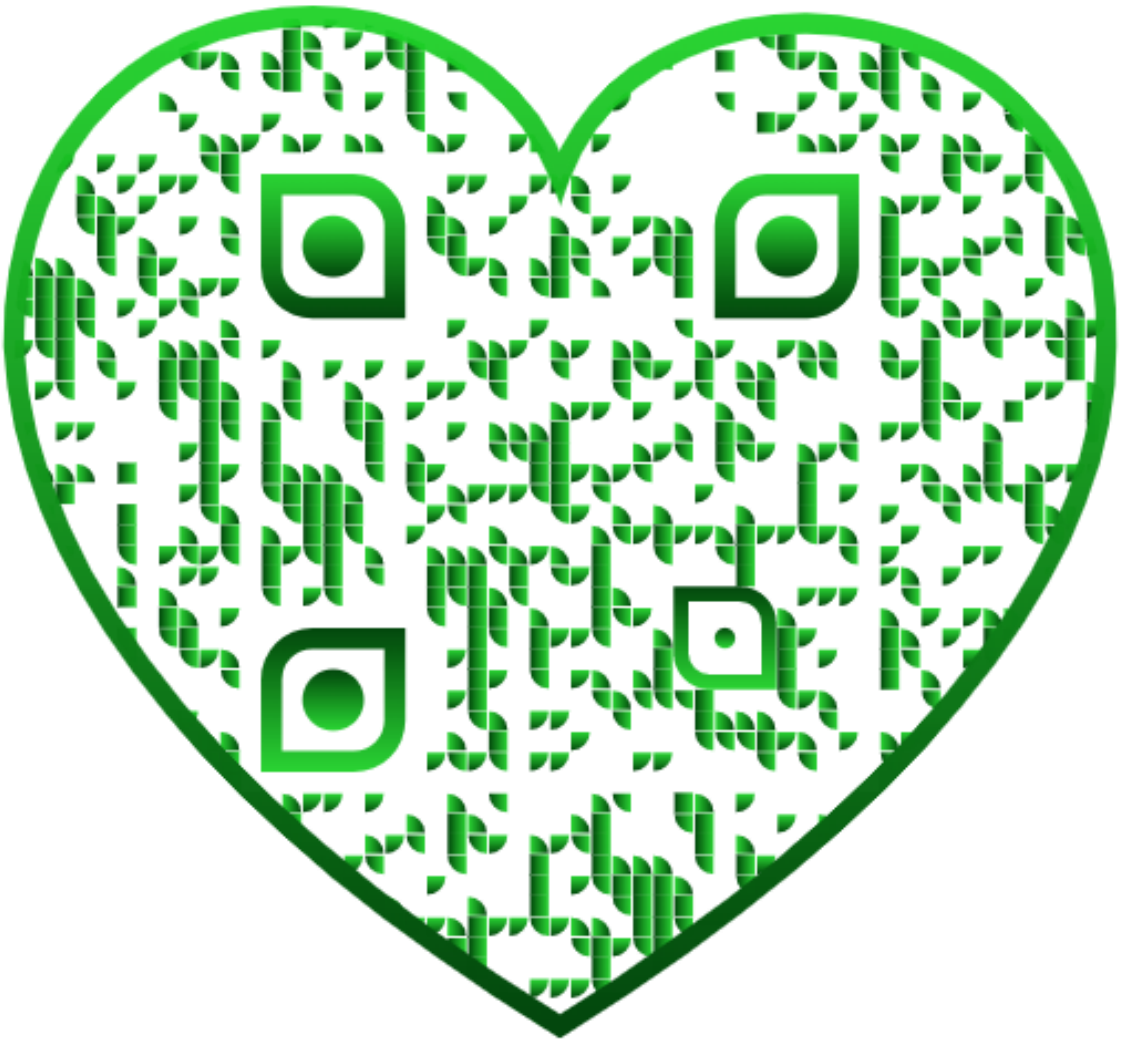
PHARMACOTHERAPY

PREPARATORY REVIEW AND RECERTIFICATION COURSE



VOL 1 | 2024 ACCP UPDATES IN THERAPEUTICS®

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American College of Clinical Pharmacy

Updates in Therapeutics®:

Pharmacotherapy Preparatory Review and Recertification Course

American College of Clinical Pharmacy

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2024 Edition
Volume 1



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Note: The authors and publisher of the Pharmacotherapy Preparatory Review and Recertification Course recognize that the development of this material offers many opportunities for error. Despite our very best efforts, some errors may persist into print. Drug dosage schedules are, we believe, accurate and in accordance with current standards. Readers are advised, however, to check other published sources to be certain that recommended dosages and contraindications are in agreement with those listed in this book. This is especially important in new, infrequently used, or highly toxic drugs.

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Continuing Pharmacy Education:
The American College of Clinical Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. The Universal Activity Numbers for the Pharmacotherapy Preparatory Review and Recertification Home Study Course, 2024 edition, are as follows: Acute Care in Cardiology, Chronic Care in Cardiology, and Anticoagulation, Activity No. 0217-0000-24-058-H01-P, 4.25 contact hours; Infectious Diseases I, Infectious Diseases II, Critical Care, and Fluids, Electrolytes, and Nutrition, Activity No. 0217-0000-24-059-H01-P, 4.25 contact hours; Psychiatry and Mental Health, Neurology, and Sexual and Reproductive Health, Activity No. 0217-0000-24-060-H01-P, 4.0 contact hours; Healthcare Systems and Population Health, Oncology Supportive Care, Pharmacokinetics, and Gastroenterology, Activity No. 0217-0000-24-061-H01-P, 4.25 contact hours; Endocrine and Metabolic Disorders, Nephrology, Geriatrics, and Pulmonology and Adult Vaccinations, Activity No. 0217-0000-24-062-H01-P, 4.75 contact hours; Pediatrics, Biostatistics, Study Designs, and Drug Information and Communication Strategies, Activity No. 0217-0000-24-063-H01-P, 4.75 contact hours. All Pharmacotherapy Preparatory Review and Recertification Course programs are application-based activities.

To earn continuing pharmacy education credit for the home-study version of the 2024 Pharmacotherapy Preparatory Review and Recertification Course, you must review all content and complete the attestation statements and course evaluations by May 29, 2027. Statements of continuing pharmacy education credit will be available at CPE Monitor within 2–3 business days after completion of this activity.

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The American College of Clinical Pharmacy (ACCP) has compiled the materials in this course book for pharmacists to use in preparing for the Board of Pharmacy Specialties (BPS) Pharmacotherapy Specialty certification examination. There is no intent or assurance that all of the knowledge on the examination will be covered in the ACCP process. Although ACCP does use the BPS Content Outline in creating the material for this course, ACCP does not know the specific content of any particular BPS examination. BPS guidelines prohibit any overlap of individuals writing the examination and developing preparatory materials. To maintain its strict, independent standards for certification, BPS does NOT endorse or provide review information, preparatory courses, or study guides for Board Certification Examinations.

Program Goals and Target Audience

The Updates in Therapeutics®: Pharmacotherapy Preparatory Review and Recertification Course is designed to help pharmacists who are preparing for the Board of Pharmacy Specialties certification examination in Pharmacotherapy as well as those seeking a general review and refresher on disease states and therapeutics. The program goals are as follows:

1. To present a high-quality, up-to-date overview of disease states and therapeutics;
2. To provide a framework to help attendees prepare for the specialty certification examination in pharmacotherapy; and
3. To offer participants an effective learning experience using a case-based approach with a strong focus on the thought processes needed to solve patient care problems in each therapeutic area.

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American College of Clinical Pharmacy

Updates in Therapeutics®:

Pharmacotherapy Preparatory Review and Recertification Course

Acute Care in Cardiology

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Acute Care in Cardiology

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Learning Objectives

1. Distinguish between the treatments for acute coronary syndrome: ST-segment elevation myocardial infarction and non–ST-segment elevation acute coronary syndrome.
2. Formulate evidence-based treatment strategies for patients with acute decompensated heart failure.
3. Devise a treatment plan for patients presenting with ventricular or life-threatening arrhythmias.
4. Differentiate between goals and treatment for hypertensive emergencies and hypertension without progressive organ damage.

Abbreviations in This Chapter

AAD	Antiarrhythmic drug
ACE	Angiotensin-converting enzyme
ACS	Acute coronary syndrome
ADHF	Acute decompensated heart failure
AF	Atrial fibrillation
aPTT	Activated partial thromboplastin time
BNP	B-type natriuretic peptide
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CO	Cardiac output
CV	Cardiovascular
DAPT	Dual antiplatelet therapy
ECG	Electrocardiogram
GI	Gastrointestinal
GP	Glycoprotein
GRACE	Global Registry of Acute Coronary Events
HF	Heart failure
HIT	Heparin-induced thrombocytopenia
ICD	Implantable cardioverter-defibrillator
LD	Loading dose
LOE	Level of evidence
LV	Left ventricle
LVEF	Left ventricular ejection fraction
MACE	Major adverse cardiovascular events
MAP	Mean arterial pressure
MI	Myocardial infarction
NSTE-ACS	Non–ST-segment elevation acute coronary syndrome
NSTEMI	Non–ST-segment elevation myocardial infarction
PCI	Percutaneous coronary intervention
SBP	Systolic blood pressure
SCD	Sudden cardiac death
SHD	Structural heart disease
STEMI	ST-segment elevation myocardial infarction
SVR	Systemic vascular resistance
SVT	Supraventricular tachycardia
UA	Unstable angina
UFH	Unfractionated heparin
VF	Ventricular fibrillation
VT	Ventricular tachycardia

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

1. A 62-year-old man presents to the emergency department (ED) with the chief concern of chest pain that woke him from sleep and radiates to his jaw. An electrocardiogram (ECG) reveals ST-segment depression in leads II, III, and aVF. His blood pressure is 112/62 mm Hg and heart rate is 60 beats/minute. Cardiac enzymes have been obtained, and the first troponin result was slightly positive. Preparations are under way to take the patient to the cardiac catheterization laboratory for evaluation. Which medication regimen is most appropriate for this patient at this time?
   A. Aspirin 325 mg, clopidogrel 600-mg loading dose (LD), and unfractionated heparin (UFH) infusion 80-unit/kg bolus, followed by 18 units/kg/hour and metoprolol 5 mg intravenously.
   B. Aspirin 81 mg; prasugrel 60-mg LD; UFH infusion 60-unit/kg bolus, followed by 12 units/kg/hour; and intravenous enalaprilat.
   C. Aspirin 325 mg, ticagrelor 180-mg LD, and UFH infusion 60-unit/kg bolus, followed by 12 units/kg/hour.
   D. Aspirin 81 mg, prasugrel 60-mg LD, nitroglycerin infusion at 10 mcg/minute, and bivalirudin 0.75-mg/kg bolus and 1.75-mg/kg/hour infusion.

2. An 81-year-old African American man (weight 90 kg) presents to the ED with chest pressure (10/10 on a pain scale). His ECG reveals ST-segment

depression in the inferior leads. His medical history is significant for hypertension and chronic kidney disease. Pertinent laboratory results are troponin 5.8 ng/L, serum creatinine (SCr) 3.7 mg/dL, and estimated creatinine clearance (eCrCl) 20 mL/minute. The patient has been given aspirin 325 mg single dose; a nitroglycerin drip, initiated at 5 mcg/minute, will be titrated to chest pain relief and blood pressure. The patient consents for cardiac catheterization after adequate hydration. Which anticoagulation strategy is most appropriate to initiate in this patient?

A. Intravenous heparin 4000-unit intravenous bolus, followed by a 1000-unit/hour continuous infusion.
B. Enoxaparin 90 mg subcutaneously every 12 hours.
C. Fondaparinux 2.5 mg subcutaneously daily.
D. Bivalirudin 67.5-mg bolus, followed by a 157-mg/hour infusion.

3. A 56-year-old man presents to the hospital with the chief concern of chest pain that was unrelieved at home with sublingual nitroglycerin. His ECG reveals ST-segment depression and T-wave inversion. Cardiac markers show an elevated troponin I. The cardiologist has requested that the patient go to the cardiac catheterization laboratory for further evaluation. The patient has a history of coronary artery disease (CAD) and had a myocardial infarction (MI) about 6 months ago. During his previous hospitalization, he was confirmed to have developed heparin-induced thrombocytopenia (HIT) after his platelet count (Plt) dropped to 40,000/mm^3 and he had a positive ELISA (enzyme-linked immunosorbent assay) upon serologic testing after his previous catheterization. Given this patient's diagnosis and history, which treatment regimen would be most appropriate during his cardiac catheterization?

A. Tirofiban.
B. Bivalirudin.
C. Enoxaparin.
D. Tenecteplase.

4. A 62-year-old man presents to the ED after several hours of chest discomfort. His ECG reveals a 1- to 2-mm ST-segment elevation with positive troponins. He has also had increasing shortness of breath and lower-extremity swelling over the past 2–3 weeks. His medical history is significant for tobacco use for 40 years, chronic obstructive pulmonary disease, diabetes, and hypertension. His blood pressure is 102/76 mm Hg and heart rate is 111 beats/minute. He has rales in both lungs and 2–3+ pitting edema in his extremities. His echocardiogram reveals an ejection fraction of 25%. After primary percutaneous coronary intervention (PCI), he is transferred to the cardiac intensive care unit. Which best describes the acute use of β-blocker therapy in this patient?

A. Give 12.5 mg of oral carvedilol within the first 24 hours.
B. Give 5 mg of intravenous metoprolol at the bedside.
C. Give 200 mg of oral metoprolol succinate at discharge.
D. Give no β-blocker at this time.

5. A 60-year-old man (weight 75 kg) presents to the ED with crushing substernal chest pain and ST-segment elevations on ECG. He has a medical history of diabetes and a 40 pack-year history of smoking. He is taken immediately to the catheterization laboratory for primary PCI, and a drug-eluting stent is placed in his left anterior descending artery. In addition to aspirin, which regimen would best maintain this patient's stent patency?

A. Clopidogrel 300-mg LD, followed by 75 mg daily for 12 months.
B. Prasugrel 60-mg LD, followed by 10 mg daily for 12 months.
C. Ticagrelor 180-mg LD, followed by 90 mg twice daily for 6 months.
D. Clopidogrel 600-mg LD, followed by 75 mg daily for 6 months.

6. A 60-year-old woman with New York Heart Association (NYHA) class IV heart failure (HF) (heart failure with reduced ejection fraction [HFrEF]) is admitted for increased shortness of breath and dyspnea at rest. Her extremities appear well perfused, but she has 3+ pitting edema in her lower extremities. Her vital signs include blood pressure 125/70 mm Hg, heart rate 92 beats/

minute, and oxygen saturation (Sao_2) 89% on 100% facemask. After initiating an intravenous diuretic, which intravenous agent is best to rapidly treat this patient's pulmonary symptoms?

A. Dobutamine.
B. Milrinone.
C. Nitroglycerin.
D. Metoprolol.

7. A 75-year-old woman admitted for pneumonia has a history of several non–ST-segment elevation myocardial infarctions (NSTEMIs). She had an episode of sustained ventricular tachycardia (VT) during this hospitalization. Her corrected QT (QTc) interval was 380 milliseconds on the telemetry. Her left ventricular ejection fraction (LVEF) was found to be 25%. Her serum potassium and magnesium were 4.6 mEq/L and 2.2 mg/dL, respectively. Which intravenous agent is most appropriate for this patient's ventricular arrhythmias?

A. Procainamide.
B. Metoprolol.
C. Magnesium.
D. Amiodarone.

8. A 53-year-old woman is admitted to the hospital after the worst headache she has ever had. Her medical history includes exertional asthma, poorly controlled hypertension, glaucoma, and hyperlipidemia. She is nonadherent to her medications and has not taken her prescribed blood pressure medications for 4 days. Vital signs include blood pressure 220/100 mm Hg and heart rate 65 beats/minute. She has retinal hemorrhaging on funduscopic examination. Which is most appropriate for this patient's hypertensive emergency?

A. Fenoldopam 0.1 mcg/kg/minute.
B. Nicardipine 5 mg/hour.
C. Labetalol 0.5 mg/minute.
D. Enalaprilat 0.625 mg intravenously every 6 hours.

9. A 52-year-old woman has a witnessed cardiac arrest in a shopping mall and is resuscitated with an automatic external defibrillator device. On electrophysiologic study, she has inducible VT. Which is most appropriate for reducing the secondary incidence of sudden cardiac death (SCD)?

A. Propafenone.
B. Amiodarone.
C. Implantable cardioverter-defibrillator (ICD).
D. Metoprolol.

10. The Sudden Cardiac Death in Heart Failure trial evaluated the efficacy of amiodarone or an ICD versus placebo in preventing all-cause mortality in ischemic and nonischemic patients with NYHA class II and III HF. There was a 7.2% absolute risk reduction and a 23% relative risk reduction in all-cause mortality at 60 months with an ICD versus placebo. Which best shows the number of patients needed to treat with an ICD to prevent one death versus placebo?

A. 1.
B. 4.
C. 14.
D. 43.

BPS Pharmacotherapy Specialty Examination Content Outline

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline, tested during the Spring 2024 window:

1. Patient-Centered Pharmacotherapy
   a. 1.1. Develop patient-centered, evidence-based pharmacotherapy plans. Subtasks: 1.1.1 – 1.1.3, 1.1.5, 1.1.6, 1.1.8, 1.1.10 – 1.1.12, 1.1.14, 1.1.15, 1.1.16.
   b. 1.2. Monitor the patient to ensure safe and effective pharmacotherapy. Subtasks: 1.2.1 – 1.2.4.
   c. 1.3. Modify pharmacotherapy plans through ongoing patient assessment. Subtasks: 1.3.1 – 1.3.5.

2. Application of Evidence to Practice and Education
   a. 2.1. Retrieve relevant information that addresses pharmacotherapy-related inquiries. Subtask: 2.1.5.
   b. 2.2. Evaluate pharmacotherapy-related literature and health information. Subtasks: 2.2.1, 2.2.3, 2.2.4, 2.2.7.

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline, tested starting Fall 2024:

1. Patient Care Specialty Areas
   a. 1A. Primary Pharmacotherapy Specialty Areas. Subtask: 1A2.

2. Therapeutics and Patient Management
   a. 2A. Treatment Planning. Subtasks: 2A1 – 2A5.
   b. 2B. Therapeutic Implementation. Subtasks: 2B1, 2B2.
   c. 2C. Treatment Outcomes and Monitoring. Subtasks: 2C1 – 2C5.

3. Professional Practice
   a. 3A. Quality of Care. Subtasks: 3A2 – 3A4.
   b. 3B. Evidence-Based Practice. Subtasks: 3B1 – 3B3.
   c. 3C. Practice Management. Subtask: 3C1.

I. ACUTE CORONARY SYNDROME

A. Definitions
1. Acute coronary syndrome (ACS) is a spectrum of conditions involving acute myocardial ischemia or infarction caused by an abrupt reduction in coronary blood flow (Figure 1).
2. This chapter will focus on the most common presentation of ACS (type 1 MI), as defined by the Fourth Universal Definition of Myocardial Infarction, which is caused by coronary thrombosis.
3 Atherogenic plaque rupture is the underlying pathophysiology for ACS, causing several prothrombotic substances to be released, which results in platelet activation and aggregation and eventual thrombus formation leading to partial or total occlusion of the coronary artery.
4. ACS can be divided into ST-segment elevation myocardial infarction (STEMI) and non–ST-segment elevation acute coronary syndrome (NSTE-ACS).
   a. STEMI
      i. Defined by characteristic symptoms of myocardial ischemia in association with persistent ST-segment elevation on ECG with positive troponins
      ii. STEMI is an indication for immediate coronary angiography to determine whether reperfusion can be done (see section C in this section, "Decision for Invasive Management").
   b. NSTE-ACS
      i. Suggested by the absence of persistent ST-segment elevation on ECG
      ii. NSTE-ACS can be divided into unstable angina (UA) and NSTEMI according to whether cardiac biomarkers of necrosis are present. UA and NSTEMI are closely related conditions whose pathogenesis and clinical presentation are similar but vary in risk and severity.
      iii. ECG abnormalities and elevated troponins in isolation are insufficient to make the diagnosis and must be interpreted in the appropriate clinical context (Table 1).
5. Optimal inhibition of thrombosis is paramount in ACS management.

B. Clinical Assessment and Initial Evaluation
1. A 12-lead ECG should be done and interpreted within 10 minutes of presentation.
   a. Serial ECGs can be done if the initial ECG is nondiagnostic.
2. Serial cardiac troponins should be obtained at presentation and every 1–3 hours for high sensitivity troponin and every 3–6 hours for conventional troponin. Troponin is typically trended to aid in diagnosis of ACS with concentrations more than the 99th percentile being indicative of myocardial injury. The duration for which to trend cardiac troponin is patient-specific and beyond the scope of this chapter.
3. At initial presentation, the clinical history, angina symptoms and equivalents, physical assessment, ECG, renal function, and cardiac troponin measurements can be integrated into an estimation of the risk of death and nonfatal cardiac ischemic events, which is useful for selecting the site of care, antithrombotic therapies, and invasive management. Risk calculators include the following:
   a. Thrombolysis in myocardial infarction (TIMI) risk score for UA/NSTEMI (available at www.timi.org) is useful in predicting 30-day and 1-year mortality in patients with NSTE-ACS.
      i. Composed of seven 1-point indicators rated on presentation; 1 point is given for each of the following: 65 or older, three or more risk factors for CAD, prior coronary stenosis 50% or greater, ST deviation on ECG, two or more anginal events in previous 24 hours, aspirin use in previous 7 days, and elevated cardiac biomarkers
      ii. Risk of mortality, new or recurrent MI, or severe recurrent ischemia through 14 days; 0–2 is low risk, 3 is intermediate risk, and 4 or more is high risk
      iii. Patients with higher risk scores (e.g., TIMI of 3 or more) have a greater benefit from therapies such as low-molecular-weight heparin, glycoprotein (GP) IIb/IIIa inhibitors, and invasive strategies.

b. The Global Registry of Acute Coronary Events (GRACE) risk model (www.outcomes-umassmed.org/grace/acs_risk2/index.html) predicts in-hospital and postdischarge mortality or MI. Patients with high GRACE risk model scores (i.e., GRACE score greater than 140) can be identified for early invasive strategies.

4. Angiographic features contributing to increasing complexity of coronary artery disease: Multivessel disease, left main or proximal left anterior descending artery lesion, chronic total occlusion, trifurcation lesion, complex bifurcation lesion, heavy calcification, severe tortuosity, aorto-ostial stenosis, diffuse disease, and narrow segments distal to lesion, thrombotic lesion, and lesion length greater than 20 mm (Circulation 2022;145:e18-114).

Table 1. ACS Definition

	Subjective Findings	Objective Findings	Extent of Injury
UA	Most commonly presents as a pressure-type chest pain that typically occurs at rest or with minimal exertion Pain usually starts in the retrosternal area and can radiate to either or both arms, neck, or jaw Pain may also present with diaphoresis, dyspnea, nausea, abdominal pain, or syncope Unexplained new-onset or increased exertional dyspnea is the most common angina equivalent Nonclassic, commonly associated symptoms of ischemia such as epigastric pain, indigestion, nausea, vomiting, diaphoresis, unexplained fatigue, and syncope may be present.[a]	ST-segment depression, T-wave inversion, or transient or nonspecific ECG changes can occur No positive biomarkers for cardiac necrosis	No myocardial injury; partial occlusion of coronary artery
NSTEMI		ST-segment depression, T-wave inversion, or transient or nonspecific ECG changes can occur Positive biomarkers (conventional or high sensitivity troponin I or troponin T)	Myocardial injury; partial occlusion of coronary artery
STEMI	Classic symptoms include worsening of pain or pressure in chest, characterized as viselike, suffocating, squeezing, aching, gripping, and excruciating, that may be accompanied by radiation	ST-segment elevation > 1 mm above baseline on ECG in two or more contiguous leads Positive biomarkers (conventional or high sensitivity troponin I or troponin T)	Myocardial necrosis; total occlusion of coronary artery

[a]Up to one-half of all MIs are silent or unrecognized, and one-third present with symptoms other than chest discomfort.

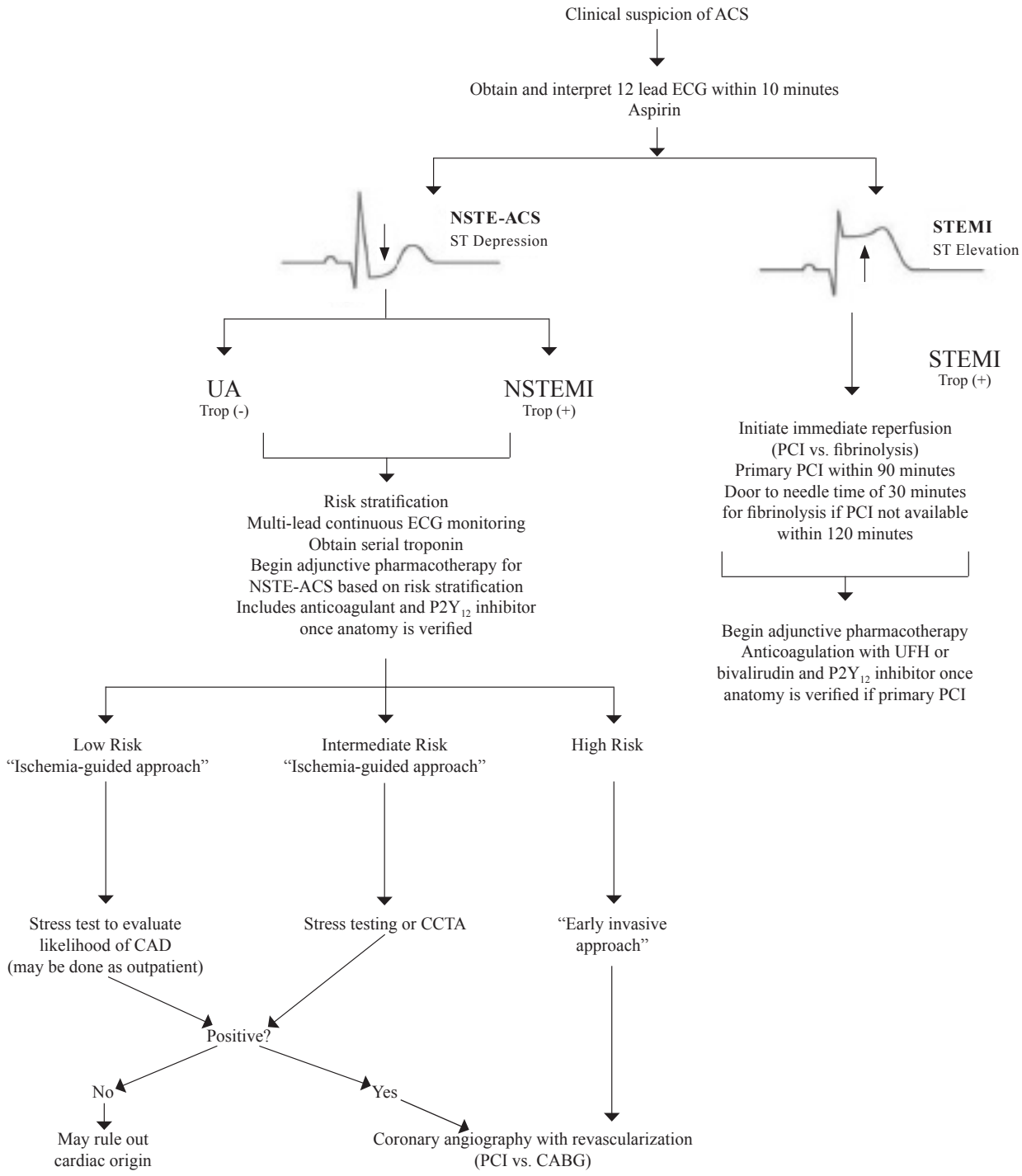


Figure 1. Acute coronary syndrome diagnosis and risk stratification.

ACS = acute coronary syndrome; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CCTA = coronary CT angiography; NSTE-ACS = non–ST-segment elevation acute coronary syndrome; NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; UA = unstable angina; UFH = unfractionated heparin.

C. Decision for Invasive Management
   1. STEMI
      a. The goal of therapy is to restore the patency of the infarct-related artery and minimize the infarct size. Secondary goals include preventing complications such as arrhythmias or death as well as controlling chest pain and associated symptoms.
      b. PCI, or coronary artery bypass grafting (CABG) if PCI not feasible, is indicated in patients with STEMI and cardiogenic shock to improve survival irrespective of time delay from MI symptom onset (Circulation 2022;145:e18-114).
      c. Primary PCI is preferred to fibrinolytic therapy. Performance measure includes goal of primary PCI within 90 minutes of first medical contact.
      d. Fibrinolytic therapy is indicated for patients with a STEMI in whom PCI cannot be done (discussed later in chapter). If PCI cannot be done within 120 minutes, performance measure for fibrinolytic administration includes a door-to-needle time of 30 minutes.
   2. NSTE-ACS
      a. The goal of therapy is to prevent total occlusion of the related artery and to control chest pain and associated symptoms. Patients with NSTE-ACS are treated on the basis of risk (TIMI, GRACE) with either an early invasive strategy (interventional approach) or an ischemia-guided strategy (a conservative management strategy using medications rather than an interventional approach).
      b. Early invasive strategy is a diagnostic angiography with intent to do revascularization, if appropriate, depending on coronary anatomy.
         i. Indicated in those with NSTE-ACS who have refractory angina or hemodynamic or electrical instability or those with high risk on the basis of clinical findings
            (a) In patients with NSTE-ACS who are initially stabilized, timing of PCI is dependent on risk for clinical events.
            (b) In patients who are initially stabilized but at high risk for clinical events, PCI may be preformed within 24 hours over a delayed invasive strategy to improve outcomes.
         ii. Routine invasive therapy is generally superior to an ischemia-guided strategy, resulting in lower rates of recurrent UA, recurrent hospitalization, MI, and death in patients with one or more of the following risk features: advanced age (older than 70), previous MI or revascularization, ST deviation, HF, depressed resting left ventricle (LV) function (i.e., LVEF less than 40%), noninvasive stress findings, high TIMI or GRACE scores, markedly elevated troponins, and diabetes.
         iii. Not recommended for those with serious comorbidities or contraindications to such procedures (hepatic, renal, pulmonary failure, cancer), and for whom the risks for the procedure may outweigh the benefits of revascularization
      c. Ischemia-guided therapy seeks to avoid the routine early use of invasive procedures unless patients have refractory or recurrent ischemic symptoms or develop hemodynamic instability.
         i. Recommended for patients with a low risk score (TIMI 0 or 1, GRACE less than 109) or intermediate risk score (TIMI 3–4, GRACE 109–140).
         ii. Indicated for those with acute chest pain with a low likelihood of ACS who are troponin negative
         iii. Can be chosen according to clinician and patient preference
   3. Patients should receive anti-ischemic and analgesic medications early in care: morphine, oxygen, nitroglycerin, and aspirin plus a β-blocker (Table 2).

Table 2. Initial Anti-ischemic and Analgesic Therapies for ACS

Therapy	Comments
M = Morphine or other narcotic analgesic	Provides analgesia and decreased pain-induced sympathetic/adrenergic tone Commonly used because it can also induce vasodilation and mediate some degree of preload and afterload reduction Morphine 1–5 mg IV every 5–30 min is reasonable if symptoms are not relieved despite maximally tolerated anti-ischemic medications[a] At least two large trials have identified an association between morphine administration and risk of death[b] Use caution in inferior (RV) infarction Slows the absorption of antiplatelet therapy, reduces time to peak antiplatelet activity, and may decrease area under the curve
O = Oxygen	Can help attenuate anginal pain secondary to tissue hypoxia Consider supplemental oxygen if Sa_{O_2} < 90%, respiratory distress, or high-risk features of hypoxemia[c] Excessive supplemental oxygen without depressed SaO_2 can be associated with increased morbidity and mortality
N = Nitroglycerin	Facilitates coronary vasodilation and may also be helpful in severe cardiogenic pulmonary edema caused by venous capacitance NTG spray or sublingual tablet (0.3–0.4 mg) every 5 min for up to three doses to relieve acute chest pain (if pain is unrelieved after one dose, call 9-1-1); afterward, assess need for IV administration[c] IV administration used in first 48 hr for persistent ischemic chest pain, HF, and HTN IV NTG 5–10 mcg/min; titrate to chest pain relief or max 200 mcg/min Use should not preclude other mortality-reducing therapies (β-blocker, ACE inhibitor) Contraindications: Sildenafil or vardenafil (use within 24 hr) or tadalafil (use within 48 hr); SBP < 90 mm Hg or ≥ 30 mm Hg below baseline, HR < 50 beats/min, HR > 100 beats/min in absence of symptomatic HF; right ventricular infarction
A = Aspirin	Inhibits platelet activation Mortality-reducing therapy Chew and swallow non–enteric coated aspirin 162–325 mg × 1 dose[c] Clopidogrel if aspirin allergy Performance measure
β-Blocker	Decrease myocardial ischemia, reinfarction, and frequency of dysrhythmias and increase long-term survival Oral β-blocker[c] should be initiated within 24 hr in patients who do not have signs of HF, evidence of low-output state, increased risk of cardiogenic shock, or other contraindications to β-blockade (e.g., PR interval > 0.24 s, second- or third-degree heart block, active asthma, or reactive airway disease) Reasonable to continue in patients with NSTE-ACS with normal LV function[a] Use metoprolol succinate, carvedilol, or bisoprolol in concomitant stabilized HFrEF[c]; add cautiously in decompensated HF Avoid agents with intrinsic sympathomimetic activity (acebutolol, pindolol) IV β-blocker[d] is potentially harmful in patients with risk factors for shock (age > 70 yr, HR > 110 beats/min, SBP < 120 mm Hg, and late presentation)

[a]Class IIb may be considered.

[b]From: Montalescot G, van't Hof AW, Lapostolle F, et al. Prehospital ticagrelor in ST-segment elevation myocardial infarction. N Engl J Med 2014;371:1016-27; and Meine TJ, Roe MT, Chen AY, et al. Association of intravenous morphine use and outcomes in acute coronary syndromes: results from the CRUSADE Quality Improvement Initiative. Am Heart J 2005;149:1043-9.

[c]Class I = should be performed or administered.

[d]Class III = not to be administered or harmful.

ACE = angiotensin-converting enzyme; ACS = acute coronary syndrome; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; HR = heart rate; HTN = hypertension; LV = left ventricle; NTG = nitroglycerin; SBP = systolic blood pressure.

4. Patients with STEMI and NSTE-ACS should be treated with antiplatelet and anticoagulant therapy (Tables 3–9).
   a. Platelets are activated by several different mechanisms, only some of which can be inhibited by medications.
   b. Combination therapy with several antiplatelet agents plus a concomitant anticoagulant is the mainstay of acute ACS management, which targets the underlying pathophysiology of thrombus formation in ACS.
   c. The roles and combinations of antiplatelet therapies continue to be refined through clinical trials in varying subsets of ACS presentation (Table 3).
   d. In general, all patients receive aspirin and $P2Y_{12}$ receptor antagonists.
   e. A minority of patients may benefit from the use of GP IIb/IIIa inhibition as bailout or provisional therapy.

Table 3. Antiplatelet Management Strategies According to ACS Presentation

Antiplatelet Agent	NSTE-ACS Ischemia Guided	NSTE-ACS Invasive	STEMI Primary PCI	STEMI + Fibrinolytic
Aspirin	Aspirin	Aspirin	Aspirin	Aspirin
$P2Y_{12}$ receptor antagonist	Clopidogrel Ticagrelor	Clopidogrel Prasugrel[a] Ticagrelor[a]	Clopidogrel Prasugrel Ticagrelor	Clopidogrel[b] Ticagrelor[c]
GP IIb/IIIa inhibitor	Greatest benefit when given to patients with high-risk features (e.g., elevated troponin), large clots, vessels with slow flow, or those not adequately pretreated with clopidogrel or TIC[d]			

[a]It may be reasonable to choose ticagrelor or prasugrel (in those who are not at high bleeding risk) over clopidogrel in patients treated with early invasive strategy for NSTE-ACS (class IIa, 2014 NSTE-ACS guideline).

[b]Pre-PCI after fibrinolytic therapy: 300-mg LD if within 24 hr of event; clopidogrel 600-mg LD if > 24 hr after event.

[c]Ticagrelor carries a Class IIb recommendation over clopidogrel, in those less than 75 years of age who undergo PCI within 24 hours of lytic therapy for STEMI.

[d]Benefit from adding GP IIb/IIIa inhibitors to aspirin therapy is greatest among those with highest-risk features (those with elevated biomarkers, those with diabetes, those undergoing revascularization) and in those not receiving adequate pretreatment with $P2Y_{12}$ inhibitor. It is reasonable (class IIa, 2014 NSTE-ACS guideline) to give GP IIb/IIIa inhibitors to high-risk patients with NSTE-ACS treated with UFH and adequately pretreated with clopidogrel.

PCI = percutaneous coronary intervention.

   f. Antiplatelet recommendations
      i. Aspirin
         (a) An irreversible cyclooxygenase-1 inhibitor blocking the formation of thromboxane A_2– and thromboxane A_2–mediated platelet activation
         (b) Given to all patients (class I)
         (c) Established first-line therapy in ACS; reduces the incidence of recurrent MI and death
         (d) LD is necessary for aspirin-naive patients; avoid enteric coated initially because of delayed and reduced absorption.
            (1) Dosing is 162–325 mg for patients at initial presentation of ACS (Table 4).
            (2) Dosing is 81–325 mg for those who are undergoing PCI, depending on chronic aspirin therapy regimen.
         (e) Aspirin is given indefinitely at a preferred dose of 81 mg after ACS with or without PCI (class I).
            (1) High dose (greater than 160 mg) is associated with more bleeding than lower dose (less than 160 mg).
            (2) High doses (greater than 160 mg) have not been shown to improve outcomes after ACS more effectively than lower doses (less than 160 mg).

(f) Dual antiplatelet therapy (DAPT) with aspirin plus a $P2Y_{12}$ receptor inhibitor is indicated for all patients after ACS for at least 12 months (see D, "Long-term Management After ACS"). The optimal aspirin dose in patients treated with DAPT appears to be 75–100 mg daily.

Table 4. Guideline Recommendations for Aspirin Therapy in ACS with or without PCI[a]

Guideline Recommendation	Class/Grade
Initiate 162–325 mg of ASA before PCI; after PCI, give 81 mg ASA	
• 2013 ACCF/AHA guideline for STEMI	I
• 2021 AHA/ACC/SCAI Guideline for Coronary Artery Revascularization	I
Initiate 81–325 mg of non–enteric-coated ASA before PCI in patients already taking ASA; in patients not taking ASA, give 325 before PCI; after PCI, continue 81 mg ASA	
• 2014 NSTE-ACS guideline	I
• 2021 AHA/ACC/SCAI Guideline for Cornonary Revascularization	I
81 mg of ASA preferred to higher maintenance doses	
• 2014 NSTE-ACS guideline	IIa
• 2013 ACCF/AHA guideline for STEMI	IIa
• 2021 AHA/ACC/SCAI Guideline for Coronary Revascularization	I

[a]Class I = should be performed or administered; class IIa = reasonable to be performed or administered; class IIb = may be considered; class III = not to be administered or harmful.

ACCF = American College of Cardiology Foundation; AHA = American Heart Association; ASA = acetylsalicylic acid; SCAI = Society for Cardiovascular Angiography and Interventions.

ii. $P2Y_{12}$ inhibitors
   (a) Inhibit the effect of adenosine diphosphate on the platelet, a key mediator resulting in amplification of platelet activation
   (b) $P2Y_{12}$ inhibitor therapy is given to all patients (class I).
   (c) Choice of oral $P2Y_{12}$ inhibitor depends on an ischemia-guided therapy or early invasive approach and pharmacokinetic differences (Tables 5–7).
      (1) Prasugrel should not be administered to patients with a history of stroke or transient ischemic attack (class III).
      (2) The efficacy of ticagrelor is decreased in patients treated with higher doses of aspirin (greater than 300 mg daily) compared with lower doses (less than 100 mg daily).
   (d) Clopidogrel and ticagrelor are preferred for a medical (i.e., ischemia-guided) strategy (Table 5).
      (1) Clopidogrel, which is characterized by a less potent and more variable platelet inhibition, may be used where ticagrelor is contraindicated, unavailable, or in those at higher risk for bleeding.
   (e) Clopidogrel, ticagrelor, and prasugrel are options for an early invasive strategy (Table 5).
      (1) It is reasonable to choose ticagrelor over clopidogrel for $P2Y_{12}$ inhibition in patients less than 75 years of age with NSTE-ACS or STEMI treated with an early invasive strategy or coronary stenting (class IIa).
      (2) It is reasonable to choose prasugrel over clopidogrel for $P2Y_{12}$ inhibition in patients with NSTE-ACS or STEMI who undergo PCI and who are not at high risk of bleeding complications and have no history of transient ischemic attack or stroke (class IIa).
         (A) Prasugrel is not an appropriate agent to preload prior to coronary angiography and should only be used once coronary anatomy is known and intent to perform PCI is confirmed.

(3) Results of the first head-to-head ISAR-REACT 5 open-label trial showed that prasugrel was superior to ticagrelor in reducing ischemic end points (6.9% vs. 9.3%, p=0.0006) without increasing bleeding risk in 4018 patients with ACS undergoing PCI; however, limitations to this study have been identified.

(f) Limited data are available on the long-term safety or efficacy of "switching" patients treated for weeks or months with a $P2Y_{12}$ inhibitor to a different $P2Y_{12}$ inhibitor. In general, when switching $P2Y_{12}$ inhibitor therapies, it is recommended to use the 2020 International Expert Consensus on Switching Platelet $P2Y_{12}$ Receptor Inhibiting Therapies.

Table 5. Guideline Recommendations for $P2Y_{12}$ Inhibitor Therapy in ACS with or without PCI

Guideline Recommendation	Class/Grade[a]
An LD of $P2Y_{12}$ receptor inhibitor may be given before PCI. (once coronary anatomy is verified). Options include: a. Clopidogrel[b] 600 mg followed by 75 mg daily; b. PRA 60 mg followed by 10 mg daily; or c. TIC 180 mg followed by 90 mg BID • 2013 ACCF/AHA guideline for STEMI • 2014 NSTE-ACS guideline	I LOE B LOE B LOE B
For patients with NSTE-ACS treated with an early invasive or ischemia-guided strategy: a. Clopidogrel 600 mg followed by 75 mg daily b. TIC 180 mg followed by 90 mg BID • 2014 NSTE-ACS guideline	I LOE B LOE B
For patients with ACS undergoing PCI, it is reasonable to use ticagrelor or prasugrel in preference to clopidogrel in order to reduce ischemic events • 2021 ACC/AHA/SCAI Guideline for Coronary Revascularization • 2014 NSTE ACS guideline	IIa LOE B
PRA should not be administered to patients with a history of TIA or stroke • 2014 NSTE-ACS guideline • 2013 ACCF/AHA guideline for STEMI	Class III

[a]Class I = should be performed or administered; class IIa = reasonable to be performed or administered; class IIb = may be considered; class III = not to be administered or harmful.

[b]Before PCI after fibrinolytic therapy: 300-mg LD if within 24 hr of event; clopidogrel 600-mg LD if > 24 hr after event.

BID = twice daily; LOE = level of evidence; TIA = transient ischemic attack.

Table 6. Comparison of Oral $P2Y_{12}$ Receptor Inhibitors

Parameter	Clopidogrel (Plavix)[a]	Prasugrel (Effient)[b]	Ticagrelor (Brilinta)[c]
Mechanism of action	Thienopyridine; inhibits ADP-mediated platelet activation at the $P2Y_{12}$ receptor	Thienopyridine; inhibits ADP-mediated platelet activation at the $P2Y_{12}$ receptor	Inhibits ADP-mediated platelet activation at the $P2Y_{12}$ receptor
Onset of platelet inhibition	300-mg LD ~6 hr 600-mg LD ~2 hr	60-mg LD ~30 min	180 mg LD ~30 min
% Platelet inhibition	30%–40%	60%–70%	60%–70%
LD	300–600 mg[d]	60 mg	180 mg
Maintenance dose	75 mg daily	10 mg daily; (5 mg if < 60 kg, BW ≥ 75 yr)	90 mg BID[e]
Metabolism	Prodrug; converted by two-step process to active metabolite involving *CYP2C19* in addition to other CYP enzymes	Prodrug; converted by one step to active metabolite by several CYP pathways	Not prodrug; reversible, noncompetitive binding; 3A4 (primary), 3A5, P-gp inhibitor
Reversible platelet binding	No	No	Yes

Table 6. Comparison of Oral $P2Y_{12}$ Receptor Inhibitors *(Cont'd)*

Parameter	Clopidogrel (Plavix)[a]	Prasugrel (Effient)[b]	Ticagrelor (Brilinta)[c]
Half-life	8 hr (metabolite)	3.7 hr (metabolite, range 2–15 hr)	7 hr (parent), 9 hr (active metabolite)
Nonresponders	Exposure to active drug affected by *CYP2C19* genetic polymorphisms	No known issues	No known issues
Drug-drug interactions, drug-disease interactions, and common nonbleeding-related AEs	PPIs inhibit *CYP2C19* (concomitant use with esomeprazole/omeprazole is discouraged on package labeling); increased bleeding with NSAIDs, OACs, O3FAs	No clinically significant drug interactions; more bleeding with NSAIDs, OACs	Careful in pulmonary disease owing to dyspnea (up to 15%) and bradycardia (can cause ventricular pauses): More bleeding with NSAIDs, OACs Strong 3A4 inhibitors increase TIC concentrations; strong 3A4 inducers decrease TIC concentrations; do not exceed 40 mg of simvastatin or lovastatin Limit aspirin to < 100 mg; monitor digoxin concentrations
Surgery hold time[f]	5 days	7 days	3–5 days
Bleeding risk	Less than PRA and TIC with standard dosing	Risk of non-CABG, spontaneous, and fatal bleeds higher than with standard-dose clopidogrel	Risk of non-CABG bleeds higher than with standard-dose clopidogrel
Box warning	*CYP2C19* polymorphisms	Age-related bleeding; CVA/TIA	Aspirin dosing > 100 mg
Contraindications	Active bleeding	Active bleeding; TIA, CVA	Active bleeding; ICH; severe hepatic disease
Landmark trials	CREDO, CURE, PCI-CURE, CLARITY, COMMIT	TRITON-TIMI 38, TRILOGY, ISAR REACT 5	PLATO, PEGASUS
FDA indication	ACS managed medically or with PCI	ACS with PCI	ACS managed medically or with PCI

[a]Administer clopidogrel indefinitely if aspirin allergy.

[b]Avoid PRA in patients with active pathologic bleeding or a history of TIA or CVA and in patients > 75 yr unless the patient has diabetes mellitus or a history of MI.

[c]Avoid TIC in patients with active pathologic bleeding or a history of ICH. Avoid aspirin doses > 100 mg daily (exception: first dose of 325 mg).

[d]A 600-mg LD results in greater, more rapid, and more reliable platelet inhibition than a 300-mg LD.

[e]Maintenance dosing of 60 mg BID is FDA approved for reducing thrombotic events after an initial 12 mo of therapy.

[f]In emergency CABG, clopidogrel and TIC should be held for at least 24 hr to minimize the risk of CABG-related bleeding.

ADP = adenosine diphosphate; AE = adverse event; BW = boxed warning; CABG = coronary artery bypass grafting; CVA = cerebrovascular accident; CYP = cytochrome P450; FDA = U.S. Food and Drug Administration; ICH = intracranial hemorrhage; NSAID = nonsteroidal anti-inflammatory drug; O3FA = omega-3 fatty acid; OAC = oral anticoagulant; P-gp = P-glycoprotein; PPI = proton pump inhibitor; PRA = Prasugrel; TIA = transient ischemic attack; TIC = ticagrelor.

iii. Intravenous $P2Y_{12}$ inhibitor

(a) Cangrelor, a direct-acting, rapidly reversible, intravenous $P2Y_{12}$ inhibitor, achieves a high level of platelet inhibition (greater than 90% with a 30-mcg/kg intravenous bolus followed by a 4-mcg/kg/minute infusion) within 5 minutes and reaches steady state within 15–30 minutes of administration.

(b) Rapid onset and offset (half-life less than 5 minutes) allows a quick, high degree of platelet inhibition with resolution of normal platelet function within 1 hour of ending treatment.

(c) In patients undergoing PCI who are $P2Y_{12}$ inhibitor naïve (or not candidates for oral therapy), intravenous cangrelor may be reasonable to reduce periprocedural ischemic events (Class IIb).
(d) Pivotal trials comparing cangrelor with clopidogrel in ACS have not shown the superiority of cangrelor; however, both the CHAMPION PHOENIX PCI and the PLATFORM trials were discontinued prematurely.
(e) Cangrelor had better efficacy than post-PCI clopidogrel with increases in minor bleeding (not major) (CHAMPION PHOENIX).
(f) Cangrelor treatment is associated with a risk of dyspnea.
(g) Cangrelor has not been studied in settings with preloaded clopidogrel or compared with prasugrel or ticagrelor.
(h) Cangrelor has a potential use as a bridge therapy after discontinuation of oral $P2Y_{12}$ inhibitors in high-risk patients undergoing CABG (JAMA 2012;307:265-74).
(i) The onset of action of both clopidogrel and prasugrel is delayed when coadministered with cangrelor, suggesting that cangrelor preferentially binds to the $P2Y_{12}$ and prevents irreversible inhibition with prasugrel and clopidogrel's active metabolite. Therefore, clopidogrel and prasugrel should not be initiated until termination of the cangrelor infusion. No such drug interaction exists with ticagrelor.
(j) Expense and lack of evidence showing superiority to other $P2Y_{12}$ inhibitors limit cangrelor's use.

iv. Intravenous GP IIb/IIIa inhibitors
(a) Block the final common pathway of platelet aggregation; achieve 80% inhibition of ex vivo platelet aggregation
(b) Double-bolus eptifibatide and high-dose bolus tirofiban are class I options for the invasive strategy (Table 7).
(c) Most, but not all, data were gathered in the era before routine $P2Y_{12}$ inhibitor use.
(d) Benefit from adding GP IIb/IIIa inhibitors to aspirin therapy is greatest among those with highest-risk features (elevated biomarkers, diabetes, undergoing revascularization) and in those not receiving adequate pretreatment with clopidogrel or ticagrelor.
(e) It is reasonable (class IIa, 2014 NSTE-ACS guideline) to give GP IIb/IIIa inhibitors to high-risk patients with NSTE-ACS treated with UFH and adequately pretreated with clopidogrel or ticagrelor.
(f) Most studies combined GP IIb/IIIa inhibitors with UFH as the anticoagulant.
(g) Upstream administration (given before PCI) has not been shown superior to delayed administration (given at time of PCI).
(1) Upstream administration is noninferior to delayed timing for reducing ischemic events.
(2) Significantly higher bleeding rates occur in those receiving upstream GP IIb/IIIa inhibitors than in those receiving delayed administration.
(3) Bolus-only GP IIb/IIIa inhibitor administration has been adopted in clinical practice but not in the practice guidelines.
(h) Common adverse events of GP IIb/IIIa inhibitors:
(1) Most common adverse effect is bleeding, with rates as low as 1.4% and as high as 10.6%, depending on length of therapy and how bleeding rates were accrued in the individual studies.
(2) Note that the smaller-molecule agents eptifibatide and tirofiban depend on renal clearance; adjustment of the infusion is recommended to decrease the risk of bleeding; monitor SCr (CrCl).

(3) All GP IIb/IIIa inhibitors can cause thrombocytopenia; monitor hemoglobin (Hgb), hematocrit (Hct), and Plt. When administered with UFH, rates of thrombocytopenia with either tirofiban or eptifibatide are no greater than with UFH alone.
(4) Secondary to their short half-life, eptifibatide and tirofiban can be reversed within a few hours by discontinuing the infusion and are preferred (class IIb) in the NSTE-ACS guideline.

Table 7. GP IIb/IIIa Inhibitor Dosing in ACS with or without PCI[a,b]

Agent	Dosing	Renal Adjustments
Eptifibatide (Integrilin)	PCI: 180 mcg/kg IVB × 2 (10 min apart); 2 mcg/kg/min initiated after first bolus for 18–24 hr[c]; ACS without PCI: Of uncertain benefit in patients adequately pretreated with a $P2Y_{12}$ receptor inhibitor; bolus used as above	If CrCl < 50 mL/min, reduce infusion by 50%; avoid in patients on hemodialysis; not studied in patients with SCr > 4 mg/dL
Tirofiban (Aggrastat)	PCI: 25 mcg/kg IVB over 3 min; then 0.15 mcg/kg/min for 18 hr	If CrCl ≤ 60 mL/min, reduce infusion by 50%

[a]Adding GP IIb/IIIa inhibitors to aspirin therapy is most beneficial in patients with high-risk features (those with elevated biomarkers, those with diabetes, those undergoing revascularization) and in those not receiving adequate pretreatment with $P2Y_{12}$ inhibitors. Administration of GP IIb/IIIa inhibitors to patients adequately treated with $P2Y_{12}$ inhibitors is of uncertain clinical benefit.

[b]GP IIb/IIIa inhibitors should be used in combination with heparin (either UFH or low-molecular-weight heparin) or used provisionally with bivalirudin.

[c]Double bolus is recommended to support PCI in STEMI and NSTE-ACS.

IVB = intravenous bolus.

v. Platelet function testing
(a) Although platelet function can be evaluated by platelet function testing or genotyping, neither is routinely done in the clinical setting.
(b) Although platelet function and genetic testing are not routine and have not been endorsed by guidelines to date, several clinical trials have offered promise with utilizing genetic information in order to optimize antiplatelet choice and outcomes.

g. Anticoagulant recommendations
i. An anticoagulant should be administered to all patients with ACS in addition to antiplatelet therapy to reduce the risk of intracoronary and catheter thrombus formation (Tables 8 and 9), irrespective of initial treatment strategy.
ii. Use of anticoagulants is typically concentrated in the procedural setting, though use may continue for a finite period after the procedure.
iii. Selection and use among agents may depend on ACS presentation, timing or dose of preprocedural antiplatelet medication, clot burden during procedure, and estimated risk of bleeding during procedure.
iv. Anticoagulants increase the risk of bleeding and will require some type of monitoring for agent-specific risks.

Table 8. Anticoagulant Management Strategies in ACS

Management Strategy	First Line Recommendations
STEMI (PPCI)	UFH, bivalirudin
STEMI, with fibrinolytic[a] therapy	UFH, enoxaparin, fondaparinux
NSTE-ACS, early invasive strategy	Enoxaparin, bivalirudin,[b] UFH
NSTE-ACS, ischemia-guided strategy	Enoxaparin, fondaparinux,[c] UFH

[a]Fibrinolytics preferred when PCI cannot be done within 120 min of first medical contact (class I). Door-to-needle time goal < 30 min. Those who receive fibrinolytic therapy should receive anticoagulation after fibrinolysis for at least 48 hr with IV UFH or IV/SC enoxaparin during hospitalization, up to 8 days (preferred, selected patients), or IV/SC fondaparinux during hospitalization, up to 8 days.

[b]If bleeding risk is high, it is reasonable to use bivalirudin monotherapy in preference to UFH plus GP IIb/IIIa inhibitor (class IIb).

[c]Fondaparinux should not be used as the sole anticoagulant to support PCI. Give additional anticoagulant during revascularization if fondaparinux was initially chosen as the anticoagulant strategy. Fondaparinux is given a class I recommendation in the 2014 NSTE-ACS guidelines (for an ischemia-guided strategy) and a class III or harmful recommendation in the 2011 PCI and 2013 STEMI guidelines when PCI is indicated.

PPCI = primary percutaneous coronary intervention; SC = subcutaneous(ly).

h. Anticoagulant agents
   i. UFH
      (a) Exerts its effects as an indirect thrombin inhibitor on fibrin-bound clots
      (b) Given as an intravenous bolus with or without infusion to reduce ischemic events; adjusted according to activated partial thromboplastin time (aPTT), anti-Xa (Anti-Xa), or activated clotting time to maintain therapeutic anticoagulation according to specific hospital protocol, usually continued for 48 hours or until PCI
         (1) Intravenous UFH: Initial bolus of 60 units/kg (maximum 4000 units)
         (2) Initial infusion of 12 units/kg/hour (maximum 1000 units/hour)
      (c) Risks include bleeding, thrombocytopenia, and HIT with or without thrombosis.
      (d) Monitoring includes aPTT or activated clotting time, Hgb/Hct, and Plt.
      (e) Unlike other anticoagulants, UFH is not renally cleared and can be used safely in those with renal impairment.
      (f) Carries Class I recommendation to reduce ischemic events for those without a history of HIT.
   ii. Enoxaparin: Molecular weight is one-third of UFH with balanced anti-factor Xa (anti-Xa) and anti-IIa activity.
      (a) Given as subcutaneous injection at least 2 inches on either side of the navel at a 90-degree angle into 1 inch of pinched skin (avoid injection into muscle); alternate dosing sites
         (1) Dosing varies depending on the reperfusion strategy and the time from the last dose to the procedure (Table 9).
         (2) 30-mg intravenous bolus given in STEMI (if age younger than 75) and in select patients with NSTE-ACS
         (3) Specific periprocedural dosing for PCI in relation to time of last subcutaneous dose (Table 9)
         (4) Decrease dosing interval to once daily when CrCl is less than 30 mL/minute.
      (b) Does not require routine anti-Xa monitoring; requires SCr to calculate CrCl for dosing; monitor Hgb, Hct, Plt
      (c) Risks include bleeding, injection site hematomas, spinal or epidural hematomas, retroperitoneal hematoma/bleeding, thrombocytopenia including HIT with or without thrombosis, mechanical prosthetic valve thrombosis (in pregnancy)

iii. Fondaparinux
  (a) Selective inhibitor of activated factor X
  (b) Longest half-life of anticoagulants (17 hours)
  (c) Given as a subcutaneous injection into fatty tissue at a 90-degree angle into a pinched skinfold; alternate dosing sites between the left and right anterolateral and posterolateral abdominal wall
    (1) Dosing NSTE-ACS: 2.5 mg subcutaneously daily, continued for the duration of hospitalization or until PCI
    (2) Not to be used as the sole anticoagulant during PCI (class III)
    (3) Contraindicated if CrCl is less than 30 mL/minute
  (d) Does not require routine anti-Xa monitoring; requires SCr to calculate CrCl to assess for contraindication; monitor Hgb, Hct, Plt
  (e) Risks include bleeding, thrombocytopenia, and spinal or epidural hematomas.
  (f) No increased risk of HIT

iv. Bivalirudin
  (a) A direct thrombin inhibitor; directly inhibits thrombin in both circulating and bound clots and inhibits thrombin-mediated platelet aggregation
  (b) Given as an intravenous bolus with fixed-rate infusion and usually continued until the end of PCI (with or without delay after infusion in some high-risk patients)
    (1) Early invasive strategy dosing: 0.1-mg/kg LD followed by 0.25 mg/kg per hour (only in patients with planned PCI), continued until diagnostic angiography or PCI
    (2) PCI dosing: 0.75-mg/kg intravenous bolus, 1.75 mg/kg/hour intravenously continued throughout the procedure
    (3) Adjust the infusion rate to 1 mg/kg/hour when the CrCl is less than 30 mL/minute or to 0.25 mg/kg/hour in patients receiving hemodialysis.
    (4) Can extend duration of infusion for up to 4 hours after procedure for prolonged antiplatelet protection
  (c) Does not require monitoring for adjustment during PCI; monitor SCr (adjustment required for infusion only in those with impaired CrCl), Hgb, Hct, Plt
  (d) Primarily reserved for patients with history of or suspected HIT undergoing PCI

i. Guideline recommendations for specific anticoagulants
  i. In an **ischemia-guided strategy**, UFH, enoxaparin, and fondaparinux are class I recommended options.
  ii. In an **invasive strategy**, UFH, enoxaparin, or bivalirudin are options.
    (a) Fondaparinux should not be used as the sole anticoagulant to support PCI (class III). An additional 85 units/kg of intravenous UFH is required immediately before PCI revascularization to reduce the risk of catheter thrombosis if fondaparinux was initially chosen as the anticoagulant strategy if no GP IIb/IIIa inhibitor is used and 60 units/kg intravenously if a GP IIb/IIIa inhibitor is used; re-bolus as needed according to target activating clotting time.
    (b) Use of enoxaparin during PCI may be reasonable in patients treated with upstream subcutaneous enoxaparin with an ischemia-guided strategy.
      (1) Patients who have received enoxaparin within 8 hours of the last subcutaneous dose generally have adequate anticoagulation to undergo PCI without supplemental bolus.
      (2) An additional dose of 0.3 mg/kg of intravenous enoxaparin should be administered at the time of PCI to patients who have received fewer than two therapeutic subcutaneous doses or who received the last subcutaneous dose 8–12 hours before PCI.
      (3) Patients who undergo PCI more than 12 hours after the last subcutaneous dose are usually treated with full-dose de novo anticoagulation with an established regimen (e.g., full-dose UFH or bivalirudin).

(c) In those at high risk of bleeding, it is reasonable to use bivalirudin monotherapy in preference to the combination of UFH and a GP IIb/IIIa receptor antagonist (class IIb).
   (1) For patients who have received UFH, wait 30 minutes and then give a 0.75-mg/kg intravenous LD, followed by a 1.75-mg/kg/hour intravenous infusion.
   (2) For patients already receiving a bivalirudin infusion, give an additional 0.5-mg/kg LD, and increase the infusion to 1.75 mg/kg/hour during PCI.

(d) Anticoagulant therapy is generally discontinued after PCI unless there is a compelling reason to continue.

iii. In patients undergoing **primary PCI**, either UFH or bivalirudin (for those with a history of HIT) is preferred.

Table 9. Antithrombotic Dosing in ACS with or without PCI

	Unfractionated Heparin (UFH)	Enoxaparin (Lovenox)	Fondaparinux (Arixtra)	Bivalirudin (Angiomax)
Classification	—	LMWH	Factor Xa inhibitor	Direct thrombin inhibitor
NSTE-ACS	60 units/kg IVB (max 4000 units), 12 units/kg/hr IV (max 1000 units/hr) for 48 hr or until PCI; goal aPTT/anti-Xa according to hospital-specific protocol	1 mg/kg SC every 12 hr for 24–48 hr or until PCI or throughout hospitalization (up to 8 days); 30 mg IVB	2.5 mg SC daily	0.1 mg/kg IVB; then 0.25 mg/kg/hr IV (only for planned invasive strategy)
PCI	Supplemental doses to target ACT[a]; if GP IIb/IIIa inhibitors, UFH 50–70 units/kg IVB; if no GP IIb IIIa inhibitors, UFH 70–100 units/kg IVB	If last dose < 8 hr, nothing additional needed; if last dose > 8 hr, 0.3 mg/kg IVB if last dose 8–12 hr before or < 2 therapeutic doses received before PCI	Fondaparinux should not be used as a sole anticoagulant for PCI	0.75 mg/kg IVB, 1.75mg/kg/hr IV d/c at end of PCI, or continue for up to 4 hr after procedure if needed; hold UFH 30 min before administration
STEMI ± primary PCI	Supplemental doses to target ACT[a]; if GP IIb/IIIa inhibitor, UFH 50–70 units/kg IVB; if no GP IIb/IIIa inhibitor, UFH 70–100 units/kg IVB	30 mg IVB, followed immediately by 1 mg/kg SC every 12 hr; do not exceed 100 mg on first two doses; if > 75 yr, omit bolus; 0.75 mg/kg SC every 12 hr; do not exceed 75 mg on first two doses	2.5 mg IVB; then 2.5 mg SC daily[b]	0.75 mg/kg IVB, 1.75 mg/kg/hr IV

Table 9. Antithrombotic Dosing in ACS with or without PCI *(Cont'd)*

	Unfractionated Heparin (UFH)	Enoxaparin (Lovenox)	Fondaparinux (Arixtra)	Bivalirudin (Angiomax)
Dose adjustments and contraindications	Avoid if history of HIT	If CrCl < 30 mL/min, 1 mg/kg SC daily; avoid if history of HIT	Contraindicated if CrCl < 30 mL/min	Adjust infusion dose in severe renal dysfunction If CrCl < 30 mL/min, reduce infusion to 1 mg/kg/hr; if on hemodialysis, reduce infusion to 0.25 mg/kg/hr

[a]Target ACT is 250–300 s for HemoTec and 300–350 s for Hemochron without GP IIb/IIIa inhibitors and 200–250 s in patients given concomitant GP IIb/IIIa inhibitors.

[b]Fondaparinux should not be used as the sole anticoagulant in PCI.

ACT = activated clotting time; CrCL = creatinine clearance; HIT = heparin-induced thrombocytopenia; IV = intravenous; IVB = intravenous bolus; LMWH = low-molecular-weight heparin; SC = subcutaneous.

5. **Fibrinolytic therapy** is indicated for patients with a STEMI in whom PCI cannot be done (Table 10).
   a. In the absence of contraindications (Table 11), fibrinolytic therapy should be given to patients with a STEMI (class I when onset of ischemic symptoms is within the previous 12 hours) when it is expected that primary PCI cannot be done within 120 minutes of first medical contact, with an ideal door-to-needle time of less than 30 minutes.
   b. When a fibrinolytic agent is given as a reperfusion strategy, UFH, enoxaparin, and fondaparinux are recommended.
   c. Patients undergoing reperfusion with fibrinolytics should receive anticoagulant therapy after fibrinolysis.
      i. UFH administration of a 60-unit/kg bolus (maximum 4000 units) and 12 units/kg/hour (maximum 1000 units/hour), to obtain an aPTT of 1.5–2.0 times control (about 50–70 seconds) for at least 48 hours
      ii. Enoxaparin 30 mg intravenously (if 75 or older, omit bolus), followed in 15 minutes by a 1-mg/kg subcutaneous injection (if 75 or older, 0.75 mg/kg) every 12 hours for the duration of index hospitalization, for up to 8 days, or until revascularization. Maximum 100 mg for the first two doses. If 75 or older, maximum 75 mg for the first two doses. If CrCl is less than 30 mL/minute, extend dosing interval to daily administration.
      iii. Fondaparinux administered with an initial 2.5-mg intravenous dose, followed in 24 hours by 2.5-mg/day subcutaneous injections (contraindicated if CrCl is less than 30 mL/minute) for the duration of the index hospitalization, for up to 8 days, or until revascularization

Table 10. Fibrinolytic Therapy

	Dosing
Alteplase (t-PA, Activase)	≤ 67 kg: 15 mg IVP over 1–2 min, then 0.75 mg/kg IV over 30 min (max 50 mg), then 0.5 mg/kg (max 35 mg) over 60 min > 67 kg: 15 mg IVP over 1–2 min, then 50 mg over 30 min, then 35 mg over 1 hr (max total dose 100 mg)
Reteplase (r-PA, Retavase)	10 units IVP; repeat 10 units IVP in 30 min
Tenecteplase (TNK-t-PA, TNKase)	< 60 kg: 30 mg IVP; 60–69 kg: 35 mg IVP; 70–79 kg: 40 mg IVP; 80–89 kg: 45 mg IVP; ≥ 90 kg: 50 mg IVP (~0.5 mg/kg)

IVP = intravenous push; r-PA = recombinant plasminogen activator; t-PA = tissue plasminogen activator.

Table 11. Contraindications to Fibrinolytic Therapy

Relative Contraindications	Absolute Contraindications
BP > 180/110 mm Hg on presentation or history of chronic poorly controlled HTN	Any prior hemorrhagic stroke
History of ischemic stroke > 3 mo before	Ischemic stroke within 3 mo (except in past 4½ hr)
Recent major surgery (< 3 wk before)	Intracranial neoplasm or arteriovenous malformation
Traumatic or prolonged CPR (> 10 min)	Active internal bleeding
Recent internal bleeding (within 2–4 wk)	Aortic dissection
Active peptic ulcer	Considerable facial trauma or closed-head trauma in past 3 mo
Noncompressible vascular punctures	Intracranial or intraspinal surgery within 2 mo
Pregnancy	Severe uncontrolled HTN (unresponsive to emergency therapy)
Known intracranial pathology (dementia)	For streptokinase,[a] treatment within previous 6 mo (if considering streptokinase again)
OAC therapy	

[a]Streptokinase is no longer marketed in the United States but is available in other countries.

BP = blood pressure; CPR = cardiopulmonary resuscitation.

D. Long-term Management After ACS
   1. DAPT
      a. Given at least 12 months after ACS
      b. DAPT reduces mortality after ACS, regardless of whether the patient received stenting.
         i. Aspirin should be continued indefinitely at a maintenance dose of 81 mg daily in all patients after ACS (class I).
         ii. In patients who were treated with an ischemia-guided therapy, aspirin plus either clopidogrel 75 mg daily or ticagrelor 90 mg twice daily should be continued for up to 12 months.
         iii. After PCI (bare metal stent or drug-eluting stent), aspirin plus clopidogrel 75 mg daily, prasugrel 10 mg daily, or ticagrelor 90 mg twice daily should be continued for at least 12 months.
      c. Early discontinuation of DAPT
         i. Early discontinuation is reasonable when the risk of morbidity exceeds the expected benefit (class IIa).
            (a) DAPT should be continued after ACS (with or without stent) for at least 12 months (class I).
            (b) Shorter-duration DAPT can be considered for patients with stable ischemic heart disease who have undergone PCI with elective stent placement (class I, 6 months duration for elective PCI).
            (c) It is reasonable to consider discontinuation of aspirin therapy after 1–3 months with continued $P2Y_{12}$ monotherapy (class IIa).
               (1) In those who are at high risk of bleeding or in those with overt bleeding, discontinuation of $P2Y_{12}$ after 6 months may be reasonable with continued aspirin (class IIb)
         ii. In general, shorter durations of DAPT are appropriate for those with a lower ischemic risk and a high bleeding risk, whereas longer-duration DAPT may be reasonable for patients with a higher ischemic risk and a lower bleeding risk.
         iii. Trials comparing shorter DAPT durations have evaluated newer-generation stents in all patients undergoing PCI (including elective cases).
            (a) In aggregate, these data support a shorter course of DAPT followed by $P2Y_{12}$ monotherapy, with a reduction in bleeding events (when compared with standard DAPT) and equivalent rates of ischemic events.

(b) The trials evaluating short-term DAPT were not powered to assess differences in stent thrombosis and few included those with STEMI.
(c) No trial has evaluated short-term DAPT followed by $P2Y_{12}$ monotherapy compared with short-term DAPT followed by aspirin monotherapy.

iv. Compared with first-generation stents, newer-generation stents have an improved safety profile and a lower risk of stent thrombosis.
v. Proton pump inhibitors can reduce the risk of gastrointestinal (GI) bleeding from DAPT.

d. Long-term DAPT
i. In general, longer-duration DAPT may be reasonable for patients at a higher ischemic risk with a lower bleeding risk.
ii. Trials evaluating the need for an extended DAPT duration (greater than 12 months) in patients with and without ACS undergoing PCI show a reduction in stent thrombosis and ischemia end points with increased bleeding for patients continued on DAPT beyond 12 months.
iii. The risk of stent thrombosis is greater on DAPT cessation; however, continued DAPT beyond 1 year is not associated with reduced cardiovascular (CV) or total mortality.
iv. A longer duration of $P2Y_{12}$ inhibitor therapy is an individualized approach according to the patient's risk of ischemia and bleeding.
(a) DAPT may be reasonable beyond 12 months if the patient is at high risk and has no significant history of bleeding while receiving DAPT (class IIb).
(b) A DAPT score derived from the DAPT study may help in deciding whether to prolong or extend DAPT in patients treated with coronary stent implantation (Table 12).
(1) Derived from the DAPT study, which included 11,648 patients with mainly clopidogrel as the $P2Y_{12}$ inhibitor
(2) For those with a high DAPT score (2 or greater), prolonged DAPT reduces net (ischemic plus bleeding) events.
(3) For those with a low DAPT score (less than 2), the benefit-risk ratio for prolonged DAPT is not favorable (increased bleeding without a reduction in ischemic events).
(4) Duration of DAPT for more or less than 12 months should jointly be made by the clinician and the patient, balancing the risks of stent thrombosis and ischemic complications with the risks of bleeding.

v. Ticagrelor has been shown to reduce CV end points of death, MI, and revascularization to a greater extent than placebo at a reduced dose of 60 mg twice daily (after at least 12 months of 90 mg twice daily) with less bleeding than extended use of 90 mg twice daily (N Engl J Med 2015;372:1791-800).

2. β-Blockers
a. Indicated for all patients unless contraindicated
b. If not initiated orally within the first 24 hours, reevaluate for possible initiation before discharge.
c. It is unclear the ideal duration of β-Blockers post-MI unless there is a compelling indication.
d. If moderate or severe LV failure, initiate carvedilol, bisoprolol, or metoprolol succinate with gradual titration. Continue indefinitely in patients with an ejection fraction less than 40%.

3. Angiotensin-converting enzyme (ACE) inhibitors
a. ACE inhibitors should be initiated and continued indefinitely for all patients with an LVEF of 40% or less and in those with hypertension, diabetes mellitus, or stable chronic kidney disease, unless contraindicated.
b. ACE inhibitors may be acceptable in all other patients with cardiac or other vascular disease.
c. Angiotensin receptor blockers (ARBs) are indicated if the patient has contraindications to or is intolerant of ACE inhibitors.
d. Contraindications include hypotension, pregnancy, and bilateral renal artery stenosis.

Table 12. DAPT Score to Determine Favorability of Prolonged DAPT

Factors Used to Calculate DAPT Score	Add Points for Total Score[a]
Age ≥ 75	-2
Age 65–74	-1
Current tobacco user	1
Diabetes mellitus	
NSTEMI or STEMI at presentation	
Prior MI or PCI	
Stent diameter < 3 mm	
Paclitaxel-eluting stent	
CHF or LVEF < 30%	2
Saphenous vein graft PCI	2

[a]A score ≥ 2 favors prolonged DAPT; a score < 2 is of unfavorable risk-benefit.

CHF = congestive heart failure; DAPT = dual antiplatelet therapy; LVEF = left ventricular ejection fraction.

Information from: Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2016;68:1082-115; and Yeh RW, Secemsky EA, Kereiakes DJ, et al. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. JAMA 2016;315:1735-49.

4. Aldosterone receptor blockers
    a. Indicated in patients who are already receiving an ACE inhibitor and β-blocker after MI and who have an LVEF of 40% or less and either symptomatic HF or diabetes, unless contraindicated with earlier administration demonstrating better outcomes than later (more than 7 days)
    b. Contraindications include hyperkalemia (potassium [K^+] 5.0 or greater), CrCl less than 30 mL/minute, and SCr greater than 2.5 mg/dL in men and greater than 2.0 mg/dL in women.
5. Lipid-lowering therapies
    a. High-intensity statins are indicated in all patients after ACS without contraindication and are generally initiated as soon as possible within the first 24 hours, preferably before planned PCI.
    b. Trials have consistently demonstrated that lower LDL-C values after ACS events are associated with lower CV death.
    c. In high-risk patients achieving a less-than-expected response to statins (LDL-C goal not obtained or less than a 50% reduction in low-density lipoprotein cholesterol [LDL]), or in those who are completely statin intolerant, non-statin therapy may be considered for CV benefit (Figure 2).
    d. Depending on the additional desired LDL percentage reduction, either ezetimibe or a PCSK9 inhibitor can be considered in combination with statin therapy in very high-risk patients.
    e. Both ezetimibe and PCSK9 inhibitors (given in combination with statins) reduce CV end points and were well tolerated, even at an extremely low LDL.
    f. PCSK9 inhibitors therapy has been associated with significant reduction of MACE in post-ACS patients. This seems to be achieved both directly through a process of modification in plaque composition with its subsequent stabilization and indirectly by intervening in lipid metabolism and platelet aggregation. Early introduction of PCSK9 inhibitor therapy for a more aggressive approach to prevent MACE may be considered given that the risk for cardiovascular events remains high within the first year of ACS, but must be weighed against cost considerations.
    g. The current treatment goal for secondary prevention (post-ACS) is an LDL less than 55 mg/dL and to achieve a greater than 50% reduction of LDL-C from baseline. In those with a second CV event within 2 years, a LDL-C goal of less than 40 mg/dL may be considered.

h. Icosapent ethyl at a dose of 2000 mg twice daily may be considered in addition to statin therapy to achieve triglyceride goal of less than 150 mg/dL for those not achieving target levels with maximally tolerated statin therapy.
i. Results of the REDUCE-IT trial demonstrated a 26% relative risk reduction (RRR) in MACE ($p< 0.01$) when ezetimibe was added to high-intensity statin therapy in those with LDL-C greater than 150 and established CVD.

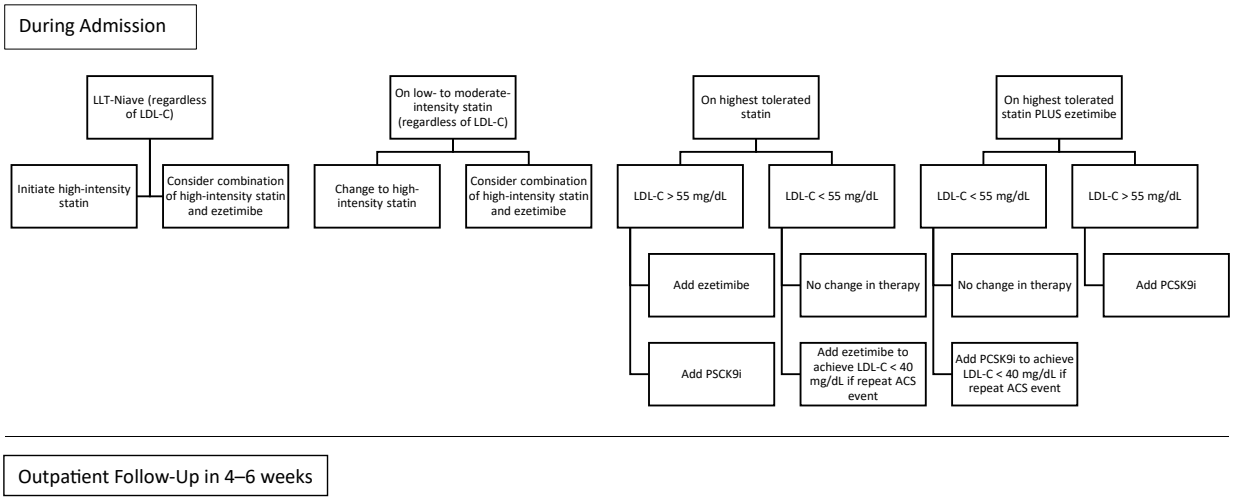

During Admission
LLT-Niave (regardless of LDL-C)
Initiate high-intensity statin
Consider combination of high-intensity statin and ezetimibe
On low- to moderate-intensity statin (regardless of LDL-C)
Change to high-intensity statin
Consider combination of high-intensity statin and ezetimibe
On highest tolerated statin
LDL-C > 55 mg/dL
Add ezetimibe
Add PSCK9i
LDL-C < 55 mg/dL
No change in therapy
Add ezetimibe to achieve LDL-C < 40 mg/dL if repeat ACS event
On highest tolerated statin PLUS ezetimibe
LDL-C < 55 mg/dL
No change in therapy
Add PCSK9i to achieve LDL-C < 40 mg/dL if repeat ACS event
LDL-C > 55 mg/dL
Add PCSK9i
Outpatient Follow-Up in 4–6 weeks

Figure 2. Lipid lowering therapy during acute coronary syndrome (ACS).
LDL-C = low-density lipoprotein cholesterol; LLT = lipid-lowering therapy.

6. Pain control
   a. NSAIDs and select cyclooxygenase-2 inhibitors (class III) should be discontinued at the time of presentation because they have been associated with an increased risk of MACE.
   b. Before discharge, the patient's musculoskeletal discomfort should be addressed, and a stepped-care approach should be used to select therapy.
   c. Pain should be treated with acetaminophen, nonacetylated salicylates, tramadol, or narcotics at the lowest dose to control symptoms.
   d. It is reasonable to use nonselective NSAIDs, such as naproxen, if initial therapy is insufficient.
      i. Monitor regularly for sustained hypertension, edema, worsening renal function, or GI bleeding.
      ii. If these occur, consider dose reduction or discontinuation.
7. Vaccination
   a. Pneumococcal vaccination is recommended for patients 65 and older and in high-risk patients (including smokers with asthma) with CV disease.
   b. An annual influenza vaccination is recommended for patients with CV disease.
8. Patient education
   a. All patients should be counseled on the duration of DAPT and the avoidance of premature discontinuation, especially in the first few days following PCI, when risk of stent thrombosis is highest.
   b. Patients should be educated about appropriate cholesterol management, blood pressure control, smoking cessation, and lifestyle management.
   c. Risk factor modification should be addressed in all patients after ACS.
9. Cardiac rehabilitation: All eligible patients should be referred to a comprehensive CV rehabilitation program.

10. Low-dose direct acting oral anticoagulant
    a. While data exist to consider the use of low-dose rivaroxaban to reduce the risk of CV mortality, MI, or stroke, current guidelines do not support routine use for patients with recent ACS.
    b. The COMPASS trial explored use for rivaroxaban 2.5 mg two times a day in addition to low dose aspirin in adults with stable CAD and found an associated absolute risk reduction of about 1% in a combined CVD endpoint, which was offset by an increased rate of major bleeding of about 1% compared with aspirin alone.

E. Special Populations
1. Antiplatelet recommendations in patients going on to CABG
    a. Aspirin should be continued preoperatively to patients undergoing CABG (81–325 mg).
    b. In patients referred for urgent CABG, clopidogrel and ticagrelor should be discontinued for at least 24 hours to reduce major bleeding.
    c. In patients referred for CABG, short-acting GP IIb/IIIa inhibitors (eptifibatide or tirofiban) should be discontinued for at least 2–4 hours before surgery to limit blood loss and transfusion.
2. Combined oral anticoagulant therapy and antiplatelet therapy in patients with atrial fibrillation (AF) undergoing PCI
    a. Triple therapy with an oral anticoagulant, low-dose aspirin, and a $P2Y_{12}$ inhibitor should be minimized because it substantially increases the risk of bleeding.
    b. New AF guidelines and consensus recommendations based on clinical trial data represent a paradigm shift from older management with triple therapy:
        i. Many trials have shown that double antithrombotic therapy (anticoagulant plus $P2Y_{12}$ inhibitor without aspirin) reduces bleeding events compared with triple therapy without signal for increasing ischemic events.
            (a) Double therapy with a $P2Y_{12}$ inhibitor plus dose-adjusted vitamin K antagonist (WOEST trial)
            (b) Double therapy with a $P2Y_{12}$ inhibitor plus rivaroxaban 15 mg daily (PIONEER AF)
            (c) Double therapy with a $P2Y_{12}$ inhibitor plus dabigatran 150 mg twice daily (RE-DUAL)
            (d) Double therapy with a $P2Y_{12}$ inhibitor plus apixaban 5 mg twice daily (AUGUSTUS)
        ii. De-escalation time from triple to dual therapy varies depending on ischemic and bleeding risks.
            (a) Aspirin therapy can be discontinued at time of discharge or can be continued for 1–3 months, depending on risks. One analysis of stent thrombosis rates suggested that 80% of events occur within 30 days of PCI; therefore, it may be reasonable to prolong aspirin therapy to 1 month to reduce the rates of stent thrombosis in those felt to be high risk.
            (b) Triple therapy may be extended beyond hospital discharge for a limited time (i.e., 1–3 months) in select patients at the highest risk of ischemic events and lowest risk of bleeding.
        iii. In AF, direct-acting oral anticoagulants are preferred to vitamin K antagonists because of their reduced bleeding risk.
            (a) Warfarin remains the drug of choice in patients with mechanical heart valves and in those with moderate to severe mitral stenosis.
            (b) If warfarin is used for triple therapy, it is reasonable to maintain the international normalized ratio (INR) at the lower end of the therapeutic range (i.e., 2–2.5).
        iv. Clopidogrel is the preferred $P2Y_{12}$ inhibitor, though ticagrelor may be reasonable in patients at high ischemic/thrombotic and low bleeding risks (i.e., avoid prasugrel).
            (a) Discontinue antiplatelet therapy at 1 year in most patients.
            (b) However, the same considerations apply for shortening the duration (i.e., 6 months in those with high bleeding risk) and extending the duration (i.e., more than 12 months in those at high thrombotic risk with low bleeding risk) as for those without AF.

   c. Proton pump inhibitors should be considered for those with a history of GI bleeding (and is reasonable in those without a known history of GI bleeding) who need greater than 2 antithrombotic agents based on the 2020 ACC Expert Consensus Pathway for Anticoagulant and Antiplatelet Therapy.
3. Older patients (i.e., 75 or older)
   a. Doses should be individualized by weight or CrCl to reduce adverse events caused by age-related changes in pharmacokinetics and dynamics, volume of distribution, comorbidities, drug interactions, and increased drug sensitivity.
   b. Bivalirudin, rather than GP IIb/IIIa inhibitors plus UFH, is reasonable in older patients, given its similar efficacy but less risk of bleeding (class IIb).
   c. If enoxaparin is used as an anticoagulant in older patients (older than 75), the bolus should be omitted, and the dosing strategy should be 0.75 mg/kg subcutaneously every 12 hours; should not exceed 75 mg for the first two doses
   d. CABG may be preferred to PCI in older patients, particularly those with diabetes mellitus or complex three-vessel disease (e.g., SYNTAX score greater than 22), with or without involvement of the proximal left anterior descending artery.
4. Chronic kidney disease
   a. CrCl should be estimated in patients with ACS, and doses of renally cleared medications should be adjusted accordingly.
   b. Patients with chronic kidney disease undergoing coronary and LV angiography should receive adequate hydration and reduced contrast volume.
5. Women
   a. Women of all ages have higher rates of in-hospital and long-term complications from ACS than men.
   b. Women derive the same benefit from aspirin, $P2Y_{12}$ inhibitors, anticoagulants, β-blockers, ACE inhibitors, and statins as men, but women may be at higher risk of adverse events.
      i. Women have a higher rate of bleeding complications, renal failure, and vascular complications.
   c. Women with NSTE-ACS and high-risk features (e.g., troponin positive) should undergo an early invasive strategy.
   d. Women with NSTE-ACS and low-risk features should not undergo early invasive treatment because of the lack of benefit and the potential for harm (class III).
   e. Hormone therapy with estrogen plus progestin, or estrogen alone, should not be initiated for secondary prevention and should not be continued in previous users unless the benefits outweigh the estimated risks.
      i. Hormone therapy increases the risk of thrombotic events, especially in the first year of therapy, and does not provide CV protection.
      ii. Women who are more than 1 year past the initiation of hormone therapy who want to continue such therapy for another compelling indication should weigh the risk-benefit, recognizing the greater risk of CV events and breast cancer (combination therapy) or stroke (estrogen).

Patient Cases

1. A 66-year-old woman (weight 70 kg) with a history of MI, hypertension, hyperlipidemia, and diabetes mellitus presents with sudden-onset diaphoresis, nausea, vomiting, and dyspnea, followed by a bandlike upper chest pain (8/10) radiating to her left arm. She had felt well until 1 month ago, when she noticed her typical angina was occurring with less exertion. Her ECG reveals ST-segment depression in leads II, III, and aVF and hyperdynamic T waves and positive cardiac enzymes. Blood pressure is 150/90 mm Hg, and all laboratory results are normal; SCr is 1.2 mg/dL. Home medications are aspirin 81 mg/day, simvastatin 40 mg every night, metoprolol 50 mg twice daily, and metformin 1 g twice daily. Which regimen is best for this patient?
   A. An early invasive approach with aspirin 325 mg, ticagrelor 180 mg one dose, and UFH 60-unit/kg bolus; then 12 units/kg/hour titrated to 50–70 seconds.
   B. An early invasive approach with aspirin 325 mg and enoxaparin 70 mg subcutaneously twice daily.
   C. An ischemia-guided strategy with tirofiban 25 mcg/kg; then 0.15 mg/kg/minute plus enoxaparin 80 mg subcutaneously twice daily, aspirin 325 mg, and clopidogrel 300 mg one dose; then 75 mg once daily.
   D. An ischemia-guided strategy with aspirin 325 mg and ticagrelor 180 mg one dose; plus UFH 70-unit/kg bolus; then 15 units/kg/hour.

2. A 45-year-old patient underwent an elective percutaneous transluminal coronary angioplasty and drug-eluting stent placement in the right coronary artery. Which best represents the minimum time DAPT should be continued?
   A. 1 month.
   B. 3 months.
   C. 6 months.
   D. 12 months.

3. A 52-year-old man (weight 100 kg) with a history of hypertension and hypertriglyceridemia presents at a major university teaching hospital with a cardiac catheterization laboratory. He has had 3 hours of crushing 10/10 substernal chest pain radiating to both arms that began while he was eating his lunch (seated), which is accompanied by nausea, diaphoresis, and shortness of breath. He has never before had chest pain of this character or intensity. He usually can walk several miles without difficulty and smokes 1.5 packs/day of cigarettes. Home medications are lisinopril 2.5 mg/day and aspirin 81 mg daily. Current vital signs include heart rate 68 beats/minute and blood pressure 178/94 mm Hg. His ECG reveals a 3-mm ST-segment elevation in leads V_2–V_4, I, and aVL. Serum chemistry values are within normal limits. The first set of cardiac markers shows positive troponins, 0.8 mcg/L (normal defined as less than 0.1 mcg/L). Which regimen is best for this patient's STEMI?
   A. Reperfusion with primary PCI with stenting, clopidogrel 300 mg one dose, aspirin 325 mg one dose, and tirofiban 25 mcg/kg followed by 0.15 mcg/kg/minute.
   B. Reperfusion with a reteplase 10-unit bolus twice (30 minutes apart), clopidogrel 300 mg one dose, aspirin 325 mg one dose, and UFH 60 unit/kg followed by 12 unit/kg/hour.
   C. Reperfusion with tenecteplase 25-mg intravenous push one dose, ticagrelor 180 mg one dose, aspirin 325 mg one dose, and bivalirudin 0.75 mg/kg followed by 1.75 mg/kg/hour.
   D. Reperfusion with primary PCI with stenting, prasugrel 60 mg one dose, aspirin 325 mg one dose, and bivalirudin 0.75 mg/kg followed by 1.75 mg/kg/hour.

Patient Cases *(Cont'd)*

4. A 76-year-old male smoker (weight 61 kg) has a history of hypertension, benign prostatic hypertrophy, and lower back pain. Three weeks ago, he began to have substernal chest pain with exertion (together with dyspnea), which radiated to both arms and was associated with nausea and diaphoresis. These episodes have increased in frequency to four or five times daily; they are relieved with rest. He has never had an ECG. Today, he awoke with 7/10 chest pain and went to the ED of a rural community hospital 2 hours later. He was acutely dyspneic and had ongoing pain. Home medications are aspirin 81 mg/day for 2 months, doxazosin 2 mg/day, and ibuprofen 800 mg three times daily. Vital signs include heart rate 42 beats/minute (sinus bradycardia) and blood pressure 104/48 mm Hg. Laboratory results include blood urea nitrogen (BUN) 45 mg/dL, SCr 2.5 mg/dL, and troponin 1.5 ng/L (normal value less than 0.1 ng/L). His ECG reveals a 3-mm ST-segment elevation. Aspirin, ticagrelor, and sublingual nitroglycerin were given in the ED. The nearest hospital with a catheterization laboratory facility is 2½ hours away. Which regimen is best?
   A. Give alteplase 15 units intravenously plus enoxaparin 30-mg intravenous bolus.
   B. Use an ischemia-guided treatment strategy with UFH 4000-unit intravenous bolus, followed by 800 units intravenously per hour.
   C. Give tenecteplase 35 mg intravenously plus UFH 4000-unit intravenous bolus followed by 800 units intravenously per hour.
   D. Transfer the patient to a facility for primary PCI.

II. ACUTE DECOMPENSATED HEART FAILURE

A. Precipitating Factors
   1. Medication related (nonadherence to medications, recent addition of negative inotropic drugs, initiation of medications that enhance salt retention, excessive alcohol or illicit drug use)
   2. Disease related (nonadherence to sodium or fluid restriction, acute myocardial ischemia, uncorrected high blood pressure, pulmonary embolus, AF or other arrhythmias, concurrent infections, other acute CV disorders)

B. Diagnosis
   1. Must include a detailed history and physical examination
   2. B-type natriuretic peptide (BNP) or NT-proBNP is useful to support the diagnosis and establish the prognosis for acute decompensated heart failure (ADHF).
      a. Useful for excluding ADHF in patients with dyspnea of unknown etiology (ADHF can be excluded when results are less than 100 pg/mL and less than 300 pg/mL, for BNP and NT-proBNP, respectively)
      b. NT-proBNP cutpoints of 450, 900, and 1800 pg/mL (for ages younger than 50, 50–75, and older than 75, respectively)
      c. May be elevated with older age, female sex, renal dysfunction, and other cardiopulmonary disorders like pulmonary embolism
      d. NT-proBNP is preferred in patients receiving angiotensin receptor neprilysin inhibitor therapy because BNP concentrations may be affected by ARNI therapy
   3. Hemodynamic monitoring (Table 13)
      a. Routine use of hemodynamic monitoring with invasive intravenous lines (e.g., Swan-Ganz pulmonary artery catheters) is not recommended; however, signs and symptoms of congestion and perfusion (Table 14) or noninvasive means to determine hemodynamic values are commonly used to determine status of decompensation.

b. Hemodynamic monitoring with pulmonary artery catheters helps in evaluating patients refractory to initial therapy, patients with unknown or unclear volume status, and patients with clinically significant hypotension or worsening renal function.
c. Use of hemodynamic monitoring for mechanical circulatory support is beyond the scope of this chapter.

Table 13. Hemodynamic Values in Patients with ADHF and Sepsis

Parameter	Normal Value	Typical ADHF Value	Typical Sepsis Value
Mean arterial pressure[a] (MAP; mm Hg)	80–100	60–80	60–80
Heart rate (HR; beats/min)	60–80	70–90	90–100
Cardiac output (CO; L/min)[b]	4–7	2–4	5–8
Cardiac index (CI; L/min/m^2)[c]	2.8–3.6	1.3–2	3.5–4
Pulmonary capillary wedge pressure (mm Hg)[d]	8–12[b]	18–30	5–8
Systemic vascular resistance (SVR; dynes/s/cm^5)[e]	900–1400	1500–3000	300–800
Central venous pressure (CVP; mm Hg)	2–6	6–15	2–6

BP = CO × SVR.
[a]MAP = diastolic blood pressure (DBP) + [⅓(SBP − DBP)].
[b]CO = stroke volume × HR.
[c]CI = CO/body surface area.
[d]15–18 mm Hg is often desired or optimal in patients with HF to ensure optimal filling pressures.
[e]SVR = [(MAP − CVP)/CO] × 80.
ADHF = acute decompensated heart failure; SVR = systemic vascular resistance.

C. Clinical Presentation
1. Patients with ADHF can be categorized into four subsets on the basis of fluid status and cardiac function (Figure 3).
2. "Wet or dry" is commonly used to describe volume status.
3. "Warm or cold" is used to describe cardiac function or ability to perfuse tissues.

Table 14. Signs and Symptoms of ADHF

Congestion (elevated PCWP)	Hypoperfusion (low CO)
Dyspnea on exertion or at rest	Fatigue
Orthopnea, paroxysmal nocturnal dyspnea	Altered mental status or sleepiness
Peripheral edema	Cold extremities
Rales	Worsening renal function
Early satiety, nausea, or vomiting	Narrow pulse pressure
Ascites	Hypotension
Hepatomegaly, splenomegaly	
Jugular venous distension	
Hepatojugular reflux	

CO = cardiac output; PCWP = pulmonary capillary wedge pressure.

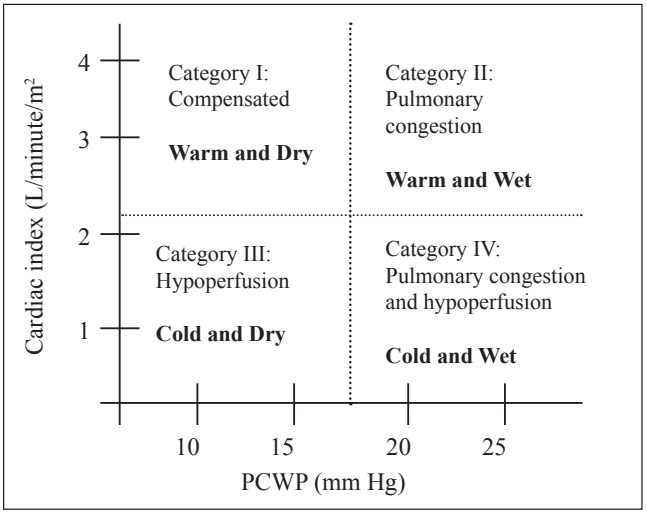


Figure 3. Forrester hemodynamic subsets based on signs and symptoms or hemodynamic parameters in acute decompensated heart failure.

PCWP = pulmonary capillary wedge pressure.

D. ADHF Therapy Overview (Box 1; Table 15)
   1. Address any precipitating factors, when possible.

Box 1. Overview of ADHF Guideline Recommendations

Diuretic therapy Recommended as IV loop diuretics for patients with fluid overload. Change to PO route on day before discharge, if possible When response to diuretics is minimal, the following options should be considered: • Fluid and sodium restriction • Initiation of increased doses or continuous infusion of loop diuretic • Addition of a second diuretic with a different mechanism of action (metolazone, chlorothiazide, acetazolamide) • Ultrafiltration
Inotropic therapy May be considered to relieve symptoms and improve end-organ function in patients with reduced LVEF and diminished peripheral perfusion or end-organ dysfunction (low output syndrome), particularly if • Marginal SBP (< 90 mm Hg) • Symptomatic hypotension despite adequate filling pressure • No response to or intolerance of IV vasodilators May be considered in similar patients with evidence of fluid overload if they respond poorly to IV diuretics or manifest diminished or worsening renal function
Vasodilator therapy May be considered in addition to IV loop diuretics to rapidly improve symptoms in patients with acute pulmonary edema or severe hypertension (if symptomatic hypotension absent) May be considered in patients with persistent symptoms despite aggressive diuretics and oral drug therapy When adjunctive therapy is necessary in addition to loop diuretics, IV vasodilators should be considered over inotropic drugs

ADHF = acute decompensated heart failure; IV = intravenous(ly); LVEF = left ventricular ejection fraction; SBP = systolic blood pressure.

2. Relieve signs and symptoms of congestion and tissue hypoperfusion.
   a. The main drug classes used to treat ADHF include diuretics, inotropes, and vasodilators.
   b. No therapy studied to date has been shown conclusively to decrease mortality.
   c. Treatments are directed toward relieving symptoms, restoring perfusion, and minimizing further cardiac damage and adverse events and are guided by cardiac output (CO) and volume status.
3. Reduce in-hospital mortality and minimize risk of rehospitalization.
4. Optimize guideline directed medical therapy (GDMT).

Table 15. General ADHF Management Based on Hemodynamic Subset[a]

Subset and Description	Treatment
Subset I: Warm and Dry (normal parameters) (PCWP 15–18 mm Hg[b] and CI > 2.2 L/min/m^2)	Optimize guideline-directed medical therapies (PO medications)
Subset II: Warm and Wet (pulmonary or peripheral congestion) (PCWP > 18 mm Hg and CI > 2.2 L/min/m^2)	IV diuretics at a dose that equals or exceeds pre-admission dose (up to 2.5-fold) ± IV vasodilators (venous[c]) for rapid relief of pulmonary congestion or (arterial) in the absence of hypotension If symptoms persist, adjunctive strategies[d] to overcome diuretic resistance may be necessary
Subset III: Cold and Dry (hypoperfusion ± orthostasis) (PCWP 15–18 mm Hg[b] and CI < 2.2 L/min/m^2)	If PCWP < 15 mm Hg, IVF until PCWP = 15–18 mm Hg If PCWP ≥ 15 mm Hg, SBP < 90 mm Hg, IV inotrope[e] If PCWP ≥ 15 mm Hg, SBP ≥ 90 mm Hg, IV vasodilator (arterial[f]) ± IV vasopressor,[g] if needed
Subset IV: Cold and Wet (pulmonary/peripheral congestion + hypoperfusion) (PCWP > 18 mm Hg and CI < 2.2 L/min/m^2)	IV diuretics + If SBP ≥ 90 mm Hg, IV vasodilator (arterial[f]) If SBP < 90 mm Hg, IV inotrope[e] ± IV vasopressor,[g] if needed

[a]Patients may be categorized into a hemodynamic subset on the basis of signs and symptoms or invasive hemodynamic monitoring.

[b]Goal PCWP is 8–12 mm Hg in a normal patient and 15–18 mm Hg in a patient with HF. If PCWP < 15 mm Hg in a patient with HF, either remove fluid restriction or cautiously administer fluids until PCWP is 15–18 mm Hg and then reassess CI.

[c]Venous vasodilator: Reduces PCWP.

[d]Adjunctive strategies for overcoming diuretic resistance include increasing the loop diuretic dose; changing to a continuous infusion; adding a diuretic with an alternative mechanism of action, an IV vasodilator, or an IV inotrope; and, in select patients, using ultrafiltration or a vasopressin antagonist.

[e]Compelling reason for inotrope = SBP < 90 mm Hg, symptomatic hypotension, or worsening renal function.

[f]Arterial vasodilator: Reduce systemic vascular resistance with compensatory increase in CI.

[g]IV vasopressors may be required when marked hypotension precludes the use of traditional IV inotropes (e.g., septic or cardiogenic shock) but are generally avoided in ADHF.

CI = cardiac index; IV = intravenous(ly); IVF = intravenous fluid; PCWP = pulmonary capillary wedge pressure; PO = oral(ly); SBP = systolic blood pressure.

E. Chronic HF Therapy in the Setting of Acute Decompensation
   1. It is recommended to continue guideline-directed medical therapies (GDMTs) during decompensation unless hemodynamic instability or contraindications exist (e.g., hypotension, cardiogenic shock) because discontinuing GDMT worsens outcomes.
      a. In patients experiencing mild decrease of renal function or asymptomatic reduction of blood pressure during HF hospitalization, diuresis and other GDMT should not routinely be discontinued (Class I).
      b. In patients with HFrEF, if discontinuation of GDMT is necessary during hospitalization, it should be reinitiated and further optimized as soon as possible (Class I).
      c. In patients with HFrEF, GDMT should be initiated during hospitalization after clinical stability is achieved (Class I).

2. ACE inhibitors/ARBs, angiotensin receptor/neprilysin inhibitor
    a. Caution with initiation or titration during aggressive diuresis
    b. Increases in SCr (decrease in glomerular filtration rate of 20% or more) from ACE inhibitor use are not associated with worse outcomes.
    c. Consider discontinuation if worsening renal function after recent drug initiation, increased symptomatic hypotension, or severe hyperkalemia (K^+ greater than 5.5 mEq/L)
3. β-Blockers
    a. Do not discontinue in patients whose condition is stable on dose before admission (i.e., recent initiation or titration was not responsible for decompensation).
        i. In OPTIMIZE-HF, discontinuation of beta blockers was associated with a higher risk of mortality compared with those continued on β blockers.
    b. Consider discontinuation if ADHF caused by recent drug initiation or increase, evidence of new or worsening low output or cardiogenic shock, symptomatic hypotension or bradycardia.
        i. Withholding or reducing β-blocker therapy should be considered in patients with marked volume overload or marginal low cardiac output.
    c. Initiation is recommended after optimization of volume status and successful discontinuation of intravenous diuretics, vasodilators, and inotropic agents.
    d. Should be initiated at a low dose only in stable, euvolemic patients
    e. Caution should be used when initiating in patients who have received inotropes during their hospital course.
4. Mineralocorticoid antagonists
    a. Do not discontinue in patients whose condition is stable on dose before admission
    b. Consider dose-reduction or discontinuation in the setting of hyperkalemia
5. SGLT2 Inhibitors
    a. Do not discontinue in patients whose condition is stable on dose before admission
    b. Temporary discontinuation for acute kidney injury when GFR falls below the cut-offs for individual use
6. Digoxin
    a. Continue at dose to achieve serum digoxin concentration of 0.5–0.8 ng/mL.
    b. Consider discontinuation in symptomatic bradycardia, life-threatening arrhythmias, elevated concentrations, or signs/symptoms of digoxin toxicity.
    c. Avoid discontinuation unless there is a compelling reason to do so, because digoxin withdrawal has been associated with worsening HF symptoms.
    d. Caution if renal function begins to deteriorate or often fluctuates

F. Diuretics (Box 2; Table 16): Used primarily to treat patients with pulmonary and peripheral congestion or wet (subset II or IV) HF
    1. In patients with HF who have fluid retention, diuretics are recommended to relieve congestion, improve symptoms, and prevent worsening heart failure.
    2. No difference between bolus and continuous administration of intravenous diuretics
    3. For patients who have been on loop diuretic therapy as an outpatient, the total daily dose should be changed to an oral furosemide equivalent and administered intravenously at 1–2.5 times the total daily dose (see conversion chart below). For patients who have not been on diuretics as an outpatient, initial furosemide dose can vary according to patients' fluid overload, kidney function, and age, and usually is about 40 to 80 mg intravenously.
    4. In patients hospitalized with HF when diuresis is inadequate to relieve symptoms and signs of congestion, it is reasonable to intensify the diuretic regimen using either higher doses of intravenous loop diuretics or addition of a second diuretic.

5. For patients with HF and congestive symptoms, addition of a thiazide (e.g., metolazone) to treatment with a loop diuretic should be reserved for patients who do not respond to moderate- or high-dose loop diuretics to minimize electrolyte abnormalities.
6. For patients requiring diuretic treatment during hospitalization for HF, the discharge regimen should include a plan for adjustment of diuretics to decrease rehospitalizations (Class I).
7. The treatment goal of diuretic use is to eliminate clinical evidence of fluid retention, using the lowest dose possible to maintain euvolemia.
8. With the exception of MRAs, the effects of diuretics on morbidity and mortality are uncertain. Therefore, diuretics should always be combined with other GDMT for HF that reduces hospitalizations and prolongs survival.

Box 2. Diuretic Therapy for ADHF

Loop diuretics (ascending limb of loop of Henle)
Most widely used and most potent, effective at low CrCl (< 30 mL/min)
Because of the threshold effect, the dose of the loop may be doubled until the desired response is achieved (e.g., urine output >500 mL in 2 hours); once threshold response is achieved, the frequency may be adjusted to meet decongestion goals, if this response is transient.
Furosemide most commonly used; furosemide 80 mg PO = furosemide 40 mg IV = bumetanide 1 mg IV or PO = torsemide 20 mg PO
Thiazides or thiazide-like diuretics (distal tubule)
Weak diuretics when used alone, less effective at low glomerular filtration rate (CrCl < 30 mL/min)
Reserved for add-on therapy when refractory to loop diuretics
Acetazolamide (proximal tubule)
Recommended as adjunct to intravenous loop diuretics
May be administered as an IV dose of 500 mg once daily to improve diuresis, naturesis, and decongestion
Diuretic resistance
Increase dose before increasing frequency of loop diuretic (note ceiling effect at ~160–200 mg of IV furosemide)
Add a second diuretic with a different mechanism of action • Metolazone 2.5–5 mg PO daily (30 min before loop diuretic administration) • Chlorothiazide 250–500 mg IV daily; consider if GI edema; generic is expensive; reserve for NPO or refractory to other alternatives
Continuous infusion of loop diuretic: Furosemide 5–20 mg/hr, up to a maximum of 40 mg/hr. IV bolus doses should be given with the start of infusion and with rate increases to achieve steady state more quickly.
Adverse effects: Electrolyte depletion (sodium, potassium, magnesium), worsening renal function

GI = gastrointestinal; NPO = nothing by mouth.

Table 16. Loop Diuretic Pharmacokinetic and Pharmacodynamic Comparisons

Drug	Furosemide	Bumetanide	Torsemide	Ethacrynic Acid
PO equivalent dose	40 mg	1 mg	20 mg	50 mg
Bioavailability, %	10%–100% (avg 50%)	80%–100%	70%–100%	100%
PO to IV conversion	2:1	1:1	1:1	1:1
Usual maintenance dose	40–160 mg	1–5 mg	10–20 mg	25–50 mg
Ceiling dose (normal CrCl)	~160 mg	1–2 mg	10–20 mg	~200 mg
Onset (peak), PO	30–60 min (1 hr)	30–60 min (1–2 hr)	60 min	30 min
Onset of action (IV)	5 min	2–3 min	10 min	5 min
Metabolism	50% renal conjugation	50% hepatic	80% hepatic	66% renal
Half-life normal (HF)	1.5–2 hr (2.7 hr)	1 hr (1.3 hr)	3–4 hr (6 hr)	1–4 hr
Avg duration of effect	6–8 hr	4–6 hr	12–16 hr	6 hr

avg = average.

G. Vasodilator Therapy (Table 17)
   1. Used (with diuretics) primarily to manage pulmonary congestion or wet (subset II or IV) HF
      a. Use is limited to relief of dyspnea in those with intact blood pressure.
      b. Vasodilator therapy may improve dyspnea symptoms and relieve pulmonary congestion; however, their benefits have not been shown to have durable effects for either rehospitalization or mortality benefit.
   2. When adequate blood pressure is maintained, use in preference to inotropic therapy.
   3. Venodilators increase venous capacitance, resulting in lower preload to reduce myocardial stress.
      a. Limits ischemia and helps preserve cardiac tissue (i.e., nitroglycerin would be the drug of choice for patients with ADHF and active ischemia)
      b. Produces rapid symptomatic benefit by reducing pulmonary congestion (i.e., acute relief of shortness of breath while awaiting the onset of diuretic effects)
      c. Nitroglycerin is commonly used as a venodilator, particularly for those with hypertension, coronary ischemia, and significant mitral regurgitation.
         i. Tachyphylaxis may develop within 24 hours, and up to 20% of those with HF may develop resistance despite increasing doses of nitroglycerin.
   4. Vasodilators with arterial vasodilating properties (nitroprusside) can also be used as an alternative to inotropes in patients with elevated systemic vascular resistance (SVR) and low CO.
      a. Sodium nitroprusside has marked potential for producing profound hypotension and is usually reserved for patients:
         i. With invasive hemodynamic monitoring (i.e., pulmonary artery catheter, arterial blood pressure monitoring)
         ii. Without end-organ dysfunction (i.e., to avoid cyanide and thiocyanate accumulation)
         iii. Avoid use in patients with active ischemia/ACS because of risk for coronary steal syndrome.
      b. Should only be used until improvement in patients hemodynamics
      c. May be used to ensure reversibility of pulmonary hypertension during evaluation for mechanical circulatory support or transplantation
      d. Nesiritide was discontinued by the manufacturer in February 2018.
   5. Vasodilators should be avoided in patients with symptomatic hypotension (i.e., systolic blood pressure [SBP] less than 90 mm Hg).
   6. Frequent blood pressure monitoring is necessary.

Table 17. Vasodilator Therapy for ADHF

	Sodium Nitroprusside (Nipride)	IV Nitroglycerin
Mechanism of action	Nitric oxide–induced stimulation of GC to convert GTP to cGMP	Combines with sulfhydryl groups in vascular endothelium to create *S*-nitrosothiol compounds that mimic nitric oxide's stimulation of GC and production of cGMP
Clinical effects	Balanced arterial and venous vasodilator	Preferential venous vasodilator greater than arterial vasodilator; arterial vasodilation at high doses
Indication	Warm and wet ADHF, alternative to inotropes in cold and wet ADHF, hypertensive crises	Warm and wet ADHF, ACS, or hypertensive crises
Dosing	0.1–0.2 mcg/kg/min IV, increase by 0.2–3 mcg/kg/min every 5 min; max dose 10 mcg/kg/min not to be used for more than 10 min	5 mcg/min IV, increase by 5 mcg/min every 5–10 min up to 200 mcg/min
Typical dose	0.5–1 mcg/kg/min IV; rarely need more than 4 mcg/kg/min	25–100 mcg/min IV, titrated to response
Half-life	2 min	1–3 min
Elimination	Cyanide hepatically metabolized, thiocyanate renally excreted	Inactive metabolites in urine
AEs	Hypotension or cyanide or thiocyanate toxicity	Hypotension, reflex tachycardia, headache, tachyphylaxis

AE = adverse effect; cGMP = cyclic guanine monophosphate; GC = guanylate cyclase; GTP = guanosine triphosphate.

H. Inotropic Therapy (Table 18)
   1. Used primarily to manage hypoperfusion or cold (subset III or IV) HF
      a. Useful for symptom relief in patients with a low SBP (less than 90 mm Hg) or symptomatic hypotension
      b. For patients in cardiogenic shock, inotropic therapy should be used to maintain systemic perfusion and preserve end-organ function (Class I).
      c. Useful in patients whose disease is refractory to other HF therapies
      d. Useful as a bridge to an LV assist device or to a heart transplant or as palliative care
   2. It is important to confirm that patients in subset III have adequate filling pressures (i.e., pulmonary capillary wedge pressure 15–18 mm Hg) before administering inotropic therapy.
   3. Given the risk of sequelae, it is reasonable to consider vasodilators before inotropes.
      a. Both milrinone and dobutamine are proarrhythmic.
      b. Inotropes increase mortality compared with vasodilator therapy.
   4. Monitor continuously for arrhythmias.
   5. Differences in the pharmacologic effects of dobutamine and milrinone may confer advantages and disadvantages, but the choice of inotropic therapy is very individualized.
      a. Milrinone may be favored:
         i. To avoid tapering or discontinuing home β-blocker
         ii. When pulmonary artery pressures are high
      b. Dobutamine may be favored in:
         i. Severe hypotension
         ii. Bradycardia
         iii. Thrombocytopenia
         iv. Severe renal impairment

Table 18. Inotropic Therapy for ADHF

	Dobutamine (Dobutrex)	Milrinone (Primacor)
Mechanism of action	β1-Agonist: Stimulates AC to convert ATP to cAMP to ↑ CO; slight peripheral vasodilation	PDE inhibitor: Inhibits cAMP breakdown in heart to ↑ CO and in vascular smooth muscle to ↓ SVR
Clinical effects	Positive inotropic, chronotropic, lusitropic effects	Positive inotropic and lusitropic effects, no direct chronotropic effects
Indication	ADHF: Cold and wet (Forester subset IV) or cold and dry exacerbations (Forester III) (if PCWP > 15 mm Hg)	
Dosing	Start 2.5–5 mcg/kg/min IV; may titrate to max of 20 mcg/kg/min	0.125–0.25 mcg/kg/min IV; may titrate to max of 0.75 mcg/kg/min
Typical dose	5 mcg/kg/min IV	No bolus, 0.1–0.375 mcg/kg/min IV
Half-life	2 min	1 hr, prolonged to 2–3 hr if HF or CrCl < 50 mL/min; may be up to 20+ hr in anuria
Elimination	Hepatically metabolized (inactive), renally eliminated	90% renal
AEs	Proarrhythmia, tachycardia, hypokalemia, myocardial ischemia, tachyphylaxis (> 72 hr); possible increased mortality with long-term use	Proarrhythmia, hypotension (avoid bolus), tachycardia, < 1% thrombocytopenia, possible increased mortality with long-term use
Other comments	Consider in severe hypotension	Consider if receiving a β-blocker or in those with high pulmonary artery pressures

AC = adenylate cyclase; AE = adverse effects; ATP = adenosine triphosphate; cAMP = cyclic adenosine monophosphate; CO = cardiac output; IV = intravenous; PDE = phosphodiesterase; SVR = systemic vascular resistance.

I. Vasopressin Antagonists
   1. Use is limited because of their significant cost and their limited effects on meaningful long-term ADHF outcomes.
      a. Should be viewed as "add on" therapy to aggressive diuresis and not as initial or adjunctive therapy for fluid removal
      b. Strict free water restriction is guideline recommended (expert opinion).
   2. Tolvaptan is FDA approved for clinically significant hyponatremia associated with HF.
      a. In those at risk of or having active cognitive symptoms despite water restriction (i.e., serum sodium less than 125 mEq/L)
      b. In those with less marked hyponatremia (i.e., less than 135 mEq/L) having neurologic symptoms and who have no correction with fluid restriction, including patients with HF and syndrome of inappropriate secretion of antidiuretic hormone
   3. Clinical use:
      a. Oral dosing: 15 mg daily; then titrated to 30–60 mg as needed
      b. Pharmacology: Binds to and inhibits the V_2 receptor, located in the renal tubule where water reabsorption is regulated
         i. Exerts its clinical effect within 2–4 hours and lasts about 24 hours
         ii. Increases serum sodium by about 2–4 mEq/L within 12–24 hours
         iii. Increases net urinary output and reduces total body weight (1–2 kg)
      c. Initiate only in the hospital setting to allow monitoring of volume status and serum sodium concentrations.
      d. An overly rapid rise in serum sodium can result in hypotension, hypovolemia, and neurologic sequelae. Maximum correction in 24 hours should be less than 8–10 mEq/L in those with chronic hyponatremia.
      e. Contraindicated with CYP3A4 inhibitors (tolvaptan is a substrate of 3A4) and in those with an eCrCl less than 10 mL/minute

f. The FDA warns against use beyond 30 days (i.e., hepatotoxicity).
g. Trials show effectiveness in correcting sodium with maintained therapy but no improvement in global clinical status or mortality and no reductions in rehospitalization.
    i. Role in long-term management of HF remains unclear.
    ii. Hyponatremia redevelops after therapy cessation.

Patient Case

Questions 5–7 pertain to the following case.

A 72-year-old man is admitted to the hospital for HF decompensation. The patient has progressively increased dyspnea when walking (now 10 ft [3 m], previously 30 ft [6 m]) and orthopnea (now four pillows, previously two pillows), increased bilateral lower-extremity swelling (3+), 13 kg of weight gain in the past 3 weeks, and dietary nonadherence. He has a history of idiopathic dilated cardiomyopathy (LVEF 25%, NYHA class III), paroxysmal AF, and hyperlipidemia. Pertinent laboratory values are as follows: BNP 2300 pg/mL (0–50 pg/mL), K^+ 4.9 mEq/L, BUN 32 mg/dL, SCr 2.0 mg/dL (baseline 1.9 mg/dL), aspartate aminotransferase (AST) 40 IU/L, alanine aminotransferase 42 IU/L, INR 1.3, aPTT 42 seconds, blood pressure 108/62 mm Hg, heart rate 82 beats/minute, and SaO_2 95%. Home medications include carvedilol 12.5 mg twice daily, lisinopril 40 mg/day, furosemide 80 mg twice daily, spironolactone 25 mg/day, and digoxin 0.125 mg/day.

5. Which regimen is best for treating his ADHF?
    A. Carvedilol 25 mg twice daily.
    B. Sodium nitroprusside 0.1 mcg/kg/min via continuous infusion.
    C. Furosemide 120 mg intravenously twice daily.
    D. Milrinone 0.5 mcg/kg/minute.

6. After being initiated on intravenous loop diuretics with only minimal urinary output, the patient is transferred to the coronary care unit for further management of diuretic-refractory decompensated HF. His SaO_2 is now 87% on a 4-L nasal cannula, and an arterial blood gas is being obtained. His blood pressure is 110/75 mm Hg and heart rate is 75 beats/minute. The patient's SCr and K^+ concentrations have begun to rise and are now 2.7 mg/dL and 5.4 mmol/L, respectively. In addition to a one-time dose of intravenous chlorothiazide, which regimen is most appropriate for this patient?
    A. Nitroglycerin 20 mcg/minute.
    B. Sodium nitroprusside 0.3 mg/kg/minute.
    C. Dobutamine 5 mcg/kg/minute.
    D. Milrinone 0.5 mcg/kg/minute.

7. The patient initially responds with 2 L of urinary output overnight, and his weight decreases by 1 kg the next day. However, by day 5, his urinary output has diminished again, and his SCr has risen to 4.3 mg/dL. He was drowsy and confused this morning during rounds. His extremities are cool and cyanotic, blood pressure is 89/58 mm Hg, and heart rate is 98 beats/minute. It is believed that he is no longer responding to his current regimen. A Swan-Ganz catheter is placed to determine further management. Hemodynamic values are cardiac index 1.5 L/minute/m^2, SVR 2650 dynes/second/cm^5, and Pulmonary capillary wedge pressure 30 mm Hg. Which regimen is most appropriate for his current symptoms?
    A. Milrinone 0.2 mcg/kg/minute.
    B. Dobutamine 10 mcg/kg/minute.
    C. Sodium nitroprusside 0.1 mcg/kg/minute.
    D. Phenylephrine 20 mcg/minute.

III. ACUTE LIFE-THREATENING ARRHYTHMIAS

A. Adult Cardiac Arrest (Figure 4)

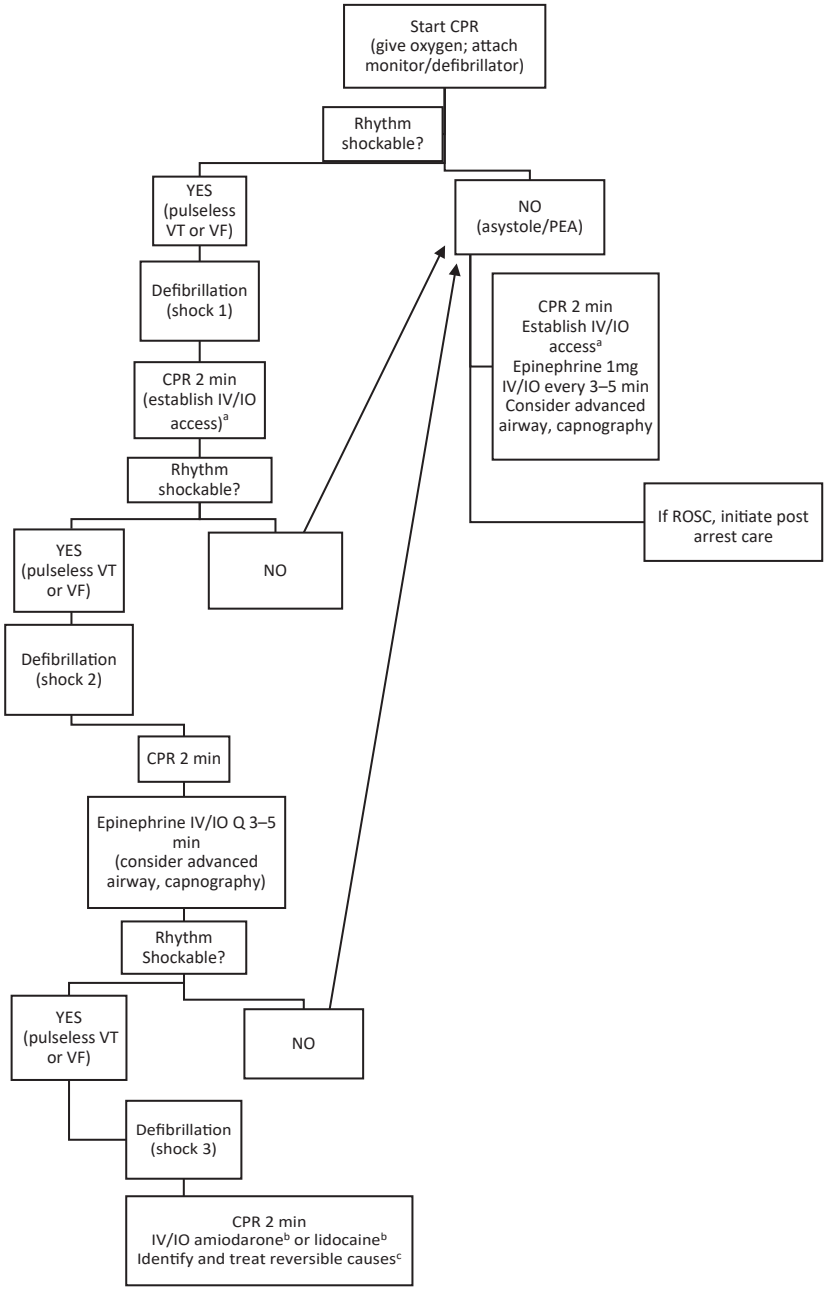


Figure 4. Adult Cardiac Arrest Algorithms

[a]If no IV/IO access, endotracheal administration of epinephrine, lidocaine, and atropine is allowed at 2–2.5 times the recommended IV/IO dose. Dilute this dose with 5–10 mL of sterile water or normal saline.

[b]Amiodarone dosing is 300 mg IV/IO ×1; may repeat with 150 mg bolus ×1. If amiodarone is unavailable, lidocaine may be considered. Lidocaine 1–1.5 mg/kg IV, repeat 0.5–0.75 mg/kg IV/IO every 5–10 min (maximum 3 mg/kg). Lidocaine has not been shown to improve ROSC and hospital admission compared with amiodarone.

[c]Hypovolemia, hypoxia, hydrogen ion (acidosis), hypokalemia or hyperkalemia, hypothermia, tension pneumothorax, tamponade (cardiac), toxins, thrombosis (pulmonary), thrombosis (coronary).

ACLS = advanced cardiac life support; CPR = cardiopulmonary resuscitation; IO = intraosseous(ly); IV = intravenous(ly); PEA = pulseless electrical activity; ROSC = return of spontaneous circulation; VF = ventricular fibrillation; VT = ventricular tachycardia.

B. Targeted Temperature Management (TTM) after cardiac arrest
   1. Indicated in adult patients who are comatose in whom return of spontaneous circulation (ROSC) has been achieved after cardiac arrest
      a. Improves neurologic outcomes after ROSC
      b. Optimal benefit for those in whom cooling begins soon after arrest
   2. Cooling process
      a. Goal temperature: 32°C–36°C based on current 2020 advanced cardiac life support guideline; however, newer data from TTM and TTM2 trials indicate fever avoidance is also reasonable.
      b. Duration: At least 24 hours after achieving the goal temperature
      c. Slowly rewarmed at a typical rate of 0.3°C/hour until core body temperature is reached
   3. Pharmacologic therapy during TTM
      a. Shivering
         i. Occurs when body temperature drops below 36°C and diminishes below 34°C
         ii. Shivering increases heat production by 600% and increases oxygen consumption and is not desirable.
         iii. Agents used to reduce shivering include meperidine, buspirone, clonidine, dexmedetomidine, and neuromuscular blocking agents.
      b. Sedation
         i. Required to minimize pain or anxiety
         ii. Agents used to provide sedation include the combination of fentanyl, midazolam, or propofol.
      c. Other adverse effects related to hypothermia
         i. Bradycardia – Lower heart rates are associated with improved outcomes; therefore, no aggressive correction is required.
         ii. Electrolyte abnormalities
            (a) Magnesium – Maintain serum magnesium concentrations at normal to high range.
            (b) Potassium – Hypokalemia is common during the hypothermic phase, whereas hyperkalemia occurs during rewarming; avoid aggressive supplementation during hypothermia.
         iii. Bleeding
            (a) Increased risk because of impaired platelet function, reduced number of platelets, impaired production of clotting enzymes, etc.
            (b) Monitor prothrombin time and aPTT once the temperature falls below 37°C.
         iv. Arrhythmias
            (a) If life-threatening arrhythmias occur during hypothermia, cooling should be discontinued.
            (b) Treatment of life-threatening arrhythmias should generally follow advanced cardiac life support principles.
         v. Hyperglycemia
            (a) Hypothermia decreases insulin sensitivity and insulin secretion from the pancreas.
            (b) Maintain blood glucose concentrations of 140–180 mg/dL during TTM.
         vi. Hypotension
            (a) Patients may require blood pressure support during TTM. Recent data from the BOX trial showed no difference in mean arterial pressure (MAP) goal of 63 mm Hg versus 77 mm Hg; however, some clinicians may use higher MAP goals greater than 80 mm Hg.
            (b) Choice of vasoactive agents depends on patient heart rate, SBP, and risk of arrhythmias.
         vii. Monitor for infection and hepatic impairment, and use adjunctive treatments as necessary.

C. Symptomatic Bradycardia
   1. If unstable, atropine 1 mg every 3–5 minutes (maximum dose 3 mg). (Note: Unstable = hypotension, acutely altered mental status, signs of shock, ischemic chest discomfort, acute HF)
   2. If atropine fails, transcutaneous pacing, dopamine 5–20 mcg/kg/minute, or epinephrine 2–10 mcg/minute

3. Isoproterenol is a β-agonist commonly used for bradyarrhythmias when pacemaker therapy is not available. It has a number of precautions for use, including coronary disease and is not currently recommended as part of the adult bradycardia algorithm.

D. Symptomatic Tachycardia
   1. If unstable, synchronized cardioversion
   2. If stable, determine whether the QRS complex is narrow or wide.
      a. Narrow-complex tachycardia (QRS less than 120 milliseconds); usually atrial arrhythmias
         i. Regular ventricular rhythm: Supraventricular tachycardia (SVT) or sinus tachycardia likely
            (a) Vagal maneuvers or adenosine 6-mg intravenous push, followed by a 20-mL saline flush, then a 12-mg intravenous push (may repeat once)
               (1) Rapid push followed by elevation of arm to increase circulation
               (2) Larger doses may be needed in patients taking theophylline or caffeine.
               (3) Initial dose should be reduced to 3 mg in patients taking dipyridamole or carbamazepine and in patients after heart transplantation, and when the drug is being given by central access.
               (4) Use adenosine cautiously in severe CAD.
               (5) Adenosine should not be given to patients with asthma.
               (6) Do not give adenosine for unstable or for irregular or polymorphic wide-complex tachycardias because it can cause degeneration to ventricular fibrillation (VF).
            (b) If vagal maneuvers or adenosine fails to convert paroxysmal SVT, calcium channel blockers (CCBs) or β-blockers can be used.
         ii. Irregular (narrow complex) ventricular rhythm: AF (or possibly atrial flutter)
            (a) General management should focus on control of the rapid ventricular rate.
               (1) Usually non-dihydropyridine CCBs (diltiazem, verapamil) or β-blockers; digoxin sometimes useful
               (2) Rate is acceptable if it is less than 110 beats/minute at rest in asymptomatic persistent AF.
            (b) If the patient is hemodynamically unstable, synchronized cardioversion is recommended.
            (c) Patients with AF for more than 48 hours are at high risk of cardioembolic events and should not be immediately cardioverted, if stable.
            (d) Transesophageal echocardiography before cardioversion is an alternative strategy to ensure the absence of left atrial clot.
            (e) Risk of thromboembolic event surrounding cardioversion (both pharmacologic and electrical) is greatest within the first 10 days.
            (f) Cardioversion
               (1) If AF for up to 7 days, either elective direct current conversion or pharmacologic cardioversion
                  (A) Flecainide, dofetilide, propafenone, ibutilide, or amiodarone (proven efficacy)
                  (B) Digoxin and sotalol are not recommended.
               (2) If AF lasts greater than 7 days, administer either elective direct current conversion or pharmacologic cardioversion with dofetilide, amiodarone, or ibutilide (proven efficacy).
      b. Wide-complex tachycardia (QRS greater than 120 milliseconds): Usually ventricular arrhythmias
         i. VT or unknown mechanism
            (a) Consider adenosine only if regular and monomorphic.
            (b) Intravenous procainamide, amiodarone (or sotalol); lidocaine second line
            (c) Avoid procainamide and sotalol if prolonged QTc.
            (d) Avoid procainamide in CHF

(e) Consider synchronized cardioversion for those with hemodynamic or clinical instability (acutely altered mental state, signs of shock, ischemic chest discomfort, acute heart failure, or hypotension)

ii. Wolff Parkinson White syndrome with atrial fibrillation
   (a) Avoid all AV nodal blocking agents, including beta-blockers, diltiazem, verapamil, digoxin, and antiarrhythmics with AV nodal blocking properties (sotalol, amiodarone, etc.).
   (b) Procainamide is drug of choice for initial therapy.

iii. Definite SVT with aberrancy: Probably transiently slowed or converted by adenosine

iv. Polymorphic (irregular) VT
   (a) Induced primarily when the QTc interval is greater than 500 milliseconds (torsades de pointes) and commonly associated with acute MI
   (b) If unstable, polymorphic (irregular) VT requires immediate defibrillation with the same strategy as VF.
   (c) If stable, intravenous magnesium 1- to 2-g intravenous bolus (maximum 16 g every 24 hours) may be given; however, this is supported only by observational studies in the setting of wide QRS.
   (d) Withdrawal of QT-prolonging medications, correction of low magnesium or K^+ concentrations
      (1) Class I and III antiarrhythmic drugs (AADs)
      (2) Assess for drug interactions by CYP3A4 (e.g., azole antifungals, erythromycin).
      (3) Assess for other QTc-prolonging drugs (e.g., haloperidol, ziprasidone, droperidol, promethazine, macrolide and quinolone antibiotics, tricyclic antidepressants, or drugs contraindicated with dofetilide such as sulfamethoxazole/trimethoprim or thiazides).

E. AAD Overview (Tables 19 and 20)

Table 19. Vaughan-Williams AAD Classes

Class/Ion Affected	Agents	Physiologic Effect	Result on Electrophysiologic Parameters	Clinical Utility
Class I/Na^+ channel blockers				
Ia (intermediate)	Disopyramide quinidine, procainamide	↓ Conduction velocity; ↑ refractory period	↑ QRS complex and ↑ QT interval	Atrial and ventricular arrhythmias
Ib (fast)	Lidocaine, mexiletine, phenytoin	↓ Conduction velocity; ↓↑ refractory period	↓ QT interval	Ventricular arrhythmias
Ic (slow)	Flecainide, propafenone	↓↓↓ Conduction velocity; Ø refractory period	↑ QRS complex	Atrial and ventricular arrhythmias
Class II β-Blockers	Metoprolol, esmolol, atenolol	↓ Conduction velocity; ↑ refractory period	↓ HR and ↑ PR interval	Atrial and ventricular arrhythmias
Class III K^+ channel blockers	Amiodarone,[a] dronedarone,[a] sotalol,[b] dofetilide, ibutilide	Ø Conduction velocity; ↑↑↑ refractory period	↑ QT interval	Atrial and ventricular arrhythmias
Class IV $Ca2^+$ channel blockers	Diltiazem, verapamil	↓ Conduction velocity; ↑ refractory period	↓ HR and ↑ PR interval	Atrial and ventricular arrhythmias

[a]Amiodarone and dronedarone have Ib, II, and IV class activity in addition to class III actions.

[b]Sotalol has 50%/50% β-blocking properties/K^+-blocking properties.

AAD = antiarrhythmic drug; $Ca2^+$ = calcium; HR = heart rate; Na^+ = sodium. ↑ = increases; ↓ = decreases; Ø = no effect.

Table 20. AAD Properties and Dosing (class I and III agents only)

Drug	AEs, Contraindications, PK, and Drug Interactions	Dosing by Indication
Class Ia: Na^+ channel blockers		
Quinidine (Quinidex, Quinaglute)	AEs: Nausea, vomiting, and diarrhea (30%), "cinchonism" (CNS and GI symptoms, tinnitus), strong vagolytic and anticholinergic properties, TdP (first 72 hr), hypotension, GI upset PK: Half-life 5–9 hr Potent inhibitor of CYP2D6; substrate and inhibitor of CYP3A4 DIs: Warfarin, digoxin	AF conversion: Avoid use because of GI AEs AF and VT maintenance: Sulfate: 200–400 mg PO every 6 hr Gluconate (CR): 324 mg PO every 8–12 hr Decrease dose by 25% if CrCl < 10 mL/min
Procainamide (Pronestyl)	AEs: Hypotension (IV use, 5%), TdP CI: LVEF < 40% PK: Active metabolite NAPA (class III effects) may accumulate in renal dysfunction	AF conversion: 1 g IV for 30 min; then 2 mg/min (1-hr efficacy 51%) AF maintenance: No oral agent available VT conversion: 20 mg/min IV up to loading dose of 17 mg/kg, arrhythmia ceases, hypotension, or QRS widens > 50% VT maintenance: 1–4 mg/min Reduce dose in renal and liver dysfunction
Disopyramide (Norpace, Norpace CR)	AEs: Anticholinergic effects, TdP, ADHF (potent negative inotropic effect) CIs: Cardiogenic shock, congenital long QT syndrome, second- or third-degree AVB, glaucoma PK: Half-life 4–8 hr Substrate of CYP2D6 DI: May enhance the effect of β-blockers	AF conversion: IR 200 mg (if < 50 kg) or 300 mg (if > 50 kg) PO every 6 hr AF maintenance: 400–800 mg/day in divided doses (recommended adult dose 600 mg/day given as IR 150 mg PO every 6 hr or as CR 300 mg PO every 12 hr) If < 50 kg, moderate renal dysfunction (CrCl > 40 mL/min) or hepatic dysfunction, max 400 mg/day If severe renal dysfunction (IR only; avoid CR) CrCl 30–40 mL/min, 100 mg every 8 hr CrCl 15–30 mL/min, 100 mg every 12 hr CrCl < 15 mL/min, 100 mg every 24 hr VT: Use has fallen out of favor because of the availability of newer agents with less toxicity
Class Ib: Na^+ channel blockers		
Lidocaine (Xylocaine)	AEs: CNS (perioral numbness, seizures, confusion, blurry vision, tinnitus) CI: Third-degree AVB PK: Reduce dose in those with HF, liver disease, low body weight, and renal dysfunction and in older adults DI: Amiodarone (increased lidocaine concentrations)	Pulseless VT/VF conversion or VT with a pulse: 1–1.5 mg/kg IVP; repeat 0.5–0.75 mg/kg every 3–5 min (max 3 mg/kg) (If LVEF < 40%, 0.5–0.75 mg/kg IVP) (Amiodarone DOC in pulseless VT/VF; lidocaine acceptable if amiodarone not available) VT maintenance: 1–4 mg/min Reduce maintenance infusion in liver disease
Mexiletine (Mexitil)	AEs: CNS (tremor, dizziness, ataxia, nystagmus) CI: Third-degree AVB PK: Half-life 12–20 hr Substrate CYP2D6, CYP1A2 Inhibitor CYP1A2	VT maintenance: 200–300 mg PO every 8 hr; max 1200 mg/day Reduce dose by 25%–30% in hepatic impairment

Table 20. AAD Properties and Dosing (class I and III agents only) *(Cont'd)*

Drug	AEs, Contraindications, PK, and Drug Interactions	Dosing by Indication
Class Ic: Na^+ channel blockers (Note: Avoid in patients with HF or after MI; increased risk of sudden death)		
Propafenone[a] (Rythmol, Rythmol SR)	AEs: Metallic taste, dizziness, ADHF, bronchospasm, bradycardia, heart block (negative inotropy and β-blocking properties) CIs: HF (NYHA III–IV), liver disease, valvular disease (TdP), CAD, MI PK: Half-life 10–25 hr Substrate CYP2D6, CYP1A2, CYP3A4 Inhibitor CYP1A2, CYP2D6 DIs: Digoxin ↑ by 70%; warfarin ↑ by 50% as well as drugs that inhibit CYP 2D6, 1A2, 3A4 (increased propafenone)	AF conversion: 600 mg PO × 1 (efficacy 45% at 3 hr) 450 mg PO × 1 (weight < 70 kg) AF maintenance: HCl: 150–300 mg PO every 8–12 hr HCl (SR): 225–425 mg PO every 12 hr Reduce dose 70%–80% in hepatic impairment
Flecainide[a] (Tambocor)	AEs: Dizziness, tremor, ADHF (negative inotropy), vagolytic, anticholinergic, hypotension CIs: HF, CAD, valvular disease, LVH (TdP) PK: Half-life 10–20 hr Substrate CYP2D6, CYP1A2 Inhibitor CYP2D6 DI: Digoxin ↑ by 25%	AF conversion: 300 mg PO × 1 (efficacy 50% at 3 hr) AF maintenance: 50–150 mg PO BID Reduce dose by 50% when CrCl < 35 mL/min
Class III: K^+ channel blockers		
Amiodarone (Cordarone)	AEs: Pulmonary fibrosis, hyperthyroidism, hypothyroidism, neurologic toxicity, GI upset, photosensitivity, corneal deposits, hepatitis, blue-gray skin, TdP, heart block, hypotension (IV), phlebitis (IV; $Ca2^+$- and β-blocking properties), bradycardia CIs: Iodine hypersensitivity, hyperthyroidism, third-degree AV heart block PK: Half-life 58 days (average) Inhibits CYP3A4/2D6/2C9/1A2/2C19 and intestinal P-gp Substrate CYP3A4/1A2/2C19/2D6 DIs: Warfarin, digoxin, statins (max simvastatin dose 20 mg/day), phenytoin ↑ ≥ 50%, lidocaine, and others Does not increase mortality in patients with HF	AF conversion: IV: 5–7 mg/kg IV over 30–60 min, then 1.2–1.8 g/day continuous IV or divided oral doses until 6–10 g PO: 1.2–1.8 g/day in divided doses until 6–10 g AF maintenance: 200–400 mg/day PO Pulseless VT/VF conversion: 300 mg or 5 mg/kg IVB in 20 mL of D_5W or NS; repeat 150 mg IVB every 3–5 min Stable VT: 150 mg IVB in 100 mL of D_5W for 10 min VT/VF maintenance: 1 mg/min × 6 hr, then 0.5 mg/min (max 2.2 g/day)
Sotalol (Betapace, Betapace AF)	AEs: ADHF, bradycardia, AVB, wheezing TdP within 3 days of initiation, bronchospasm (β-blocking effects) CIs: Baseline QTc > 440 ms or CrCl < 40 mL/min (AF only), LVEF < 40% PK: Renally eliminated, half-life 30–40 hr Hospitalization ideal for initiation of therapy because of BW: Do not initiate if baseline QTc interval > 450 ms; if QTc > 500 ms during therapy, reduce the dose, or discontinue use Not effective for AF conversion Recent data to support rapid initiation with reduced length of stay based on protocol using IV sotalol.	AF maintenance (based on CrCl): 80 mg PO BID (> 60 mL/min) 80 mg PO daily (40–60 mL/min) CI < 40 mL/min VT maintenance (based on CrCl): 80 mg PO BID (> 60 mL/min) 80 mg PO daily (30–60 mL/min) 80 mg PO every 36–48 hr (10–30 mL/min) 80 mg PO: Individualize; every 48 hr minimum (< 10 mL/min) IV dosing depends on target oral dose and creatinine clearance.

Table 20. AAD Properties and Dosing (class I and III agents only) *(Cont'd)*

Drug	AEs, Contraindications, PK, and Drug Interactions	Dosing by Indication
Class III: K^+ channel blockers		
Dofetilide (Tikosyn)	AEs: TdP (0.8%; 4% if no renal adjustment), diarrhea CIs: Baseline QTc > 440 ms or CrCl < 20 mL/min or, CI in patients with intraventricular conduction delays with baseline QT > 500 msec; NTE 550 msec PK: Renal and hepatic elimination Half-life 6–10 hr Substrate CYP3A4 DIs: CYP3A4 inhibitors and drugs secreted by kidney (cimetidine, ketoconazole, verapamil, trimethoprim, prochlorperazine, dolutegravir, megestrol), HCTZ BW: Hospitalization mandatory for initiation, obtain QTc 2–3 hr after each of the first five doses, reduce 50% if QTc ↑ > 15%; NTE QTc > 500 ms Does not increase mortality in patients with HF	AF conversion (based on CrCl calculated with actual body weight; efficacy 12% at 1 mo): 500 mcg PO BID (> 60 mL/min) 250 mcg PO BID (40–60 mL/min) 125 mcg PO BID (20–39 mL/min) CI < 20 mL/min AF maintenance: Dose as above according to renal function; adjust for QTc NTE 500 ms or > 15% ↑ in QTc
Ibutilide (Corvert)	AEs: TdP 8%, AV heart block (β-blocking properties) CIs: Baseline QTc > 440 ms, LVEF < 30%, concomitant AADs PK: Half-life 2–12 hr (average 6 hr) DIs: CYP3A4 inhibitors or QT-prolonging drugs ECG monitoring during and 4 hr after DCC	AF conversion: 1 mg IV (≥ 60 kg) or 0.01 mg/kg IV (< 60 kg); repeat in 10 min if ineffective (efficacy 47% at 90 min) BW: Potentially fatal arrhythmias (e.g., polymorphic VT) can occur with ibutilide, usually in association with TdP; patients with chronic AF may not be the best candidates for ibutilide conversion
Dronedarone (Multaq)	AEs: Worsening HF, QT prolongation, hypokalemia or hypomagnesemia with K^+-sparing diuretics, hepatic failure CIs: QTc ≥ 500 ms or PR ≥ 280 ms, NYHA class IV HF or NYHA class II–III HF with recent ADHF, severe hepatic impairment, second- or third-degree AVB, or HR < 50 beats/min PK: Half-life 13–19 hr Substrate 3A4 Inhibitor intestinal P-gp DIs: CYP3A4 inhibitors, QT-prolonging drugs, simvastatin, tacrolimus/sirolimus, warfarin, and other CYP3A4 substrates with narrow therapeutic range, digoxin and other P-gp substrates (dabigatran, rivaroxaban)	AF maintenance: 400 mg orally BID Discontinue if QTc ≥ 500 ms BW: Risk of death is doubled when used in patients with symptomatic HF with recent decompensation necessitating hospitalization or NYHA class IV symptoms; use is contraindicated in these patients Use in patients with permanent AF doubles the risk of death, stroke, and hospitalization for HF; use is contraindicated in patients with AF who will not or cannot be converted to normal sinus rhythm

[a]Indicates that pill-in-pocket approach can be used for selected patients.

AE = adverse effect; AV = atrioventricular; AVB = atrioventricular block; BID = twice daily; BW = boxed warning CAD = coronary artery disease; CI = contraindication; CNS = central nervous system; CR = controlled release; DCC = direct current cardioversion; D_5W = dextrose 5%; DI = drug interaction; DOC = drug of choice; GI = gastrointestinal; HCl = hydrochloride; HCTZ = hydrochlorothiazide; HR = heart rate; IR = immediate release; IV = intravenously; LVH = left ventricular hypertrophy; ms = millisecond(s); NAPA = *N*-acetylprocainamide; NS = normal saline; NTE = not to exceed; NYHA = New York Heart Association; PK = pharmacokinetics; PO = by mouth; QTc = corrected QT interval; SR = sustained release; TdP = torsades de pointes; VF = ventricular fibrillation; VT = ventricular tachycardia.

F. Long-term Management of Ventricular Arrhythmias
   1. Nonsustained VT
      a. Asymptomatic
         i. Infrequent ventricular ectopic beats, couplets, and triplets without other signs of underlying structural heart disease (SHD) or inherited arrhythmia syndrome should be considered a normal variant in asymptomatic patients.
         ii. No treatment other than reassurance is needed for patients without SHD or inherited arrhythmia disorder.
         iii. Treat survivors of MI and HFrEF with β-blockers (class I), unless contraindicated.
      b. Symptomatic
         i. β-Blockers may be considered for a therapeutic trial in symptomatic patients (class IIb, level of evidence [LOE] C).
         ii. Non-dihydropyridine CCBs may be considered as an alternative to β-blocker therapy in suitable patients without SHD.
         iii. AAD therapy (amiodarone, flecainide, mexiletine, propafenone, sotalol) may be considered to improve symptoms associated with arrhythmias in patients receiving adequate doses of a β-blocker or calcium channel blocker (CCB) (class IIb; LOE C).
            (a) Flecainide and propafenone are not recommended to suppress premature ventricular contractions in patients with reduced LV function (class III).
            (b) Sotalol should be used with caution in patients with chronic kidney disease and should be avoided in patients with a prolonged QT interval at baseline or excessive prolongation of QT interval (500 milliseconds) on therapy initiation (class I; LOE B).
            (c) Amiodarone appears to have less overall proarrhythmic risk than other AADs in patients with HF and may be preferred to other membrane-active AADs unless a functioning defibrillator has been implanted (class IIb; LOE C).
         iv. Amiodarone, sotalol, and other β-blockers are useful after defibrillator implantation to reduce shocks and suppress nonsustained VT in patients who are unsuitable for ICD therapy, in addition to optimal medical therapy for patients with HF.
   2. Sustained VT
      a. Immediate defibrillation for pulseless VT
      b. Synchronized cardioversion for VT with pulse
      c. Evaluate cardiac structure and function.
      d. ICD indicated for most patients with SHD

G. Implantable Cardioverter-Defibrillators
   1. For primary prevention of SCD
      a. LVEF of 35% or less that is caused by ischemic heart disease who are at least 40 days post-MI and at least 90 days postrevascularization, and with NYHA class II or III HF despite GDMT
      b. In patients with LVEF of 30% or less that is caused by ischemic heart disease who are at least 40 days post-MI and at least 90 days postrevascularization, and with NYHA class I HF despite GDMT
      c. Nonischemic cardiomyopathy, HF with NYHA class II–III symptoms, and an LVEF of 35% or less, despite at least 3 months of GDMT
      d. Syncope with SHD and inducible VT/VF during electrophysiologic study
      e. High risk of life-threatening VT/VF; congenital long QT syndrome with recurrent symptoms or torsades de pointes while receiving a β-blocker
      f. Must have reasonable survival expectation for more than 1 year

2. For secondary prevention of SCD
    a. Previous episode of resuscitated VT/VF, hemodynamically unstable VT with no completely reversible cause, or sustained VT in presence of heart disease
    b. Should receive optimal chronic medications (β-blockers, ACE inhibitors) unless contraindicated
    c. Must have reasonable survival expectation for more than 1 year
3. General medication considerations with ICD
    a. β-Blockers
        i. Considered mainstay therapy
        ii. Effective in suppressing ventricular ectopic beats and in reducing SCD in a spectrum of cardiac disorders in patients with and without HF (nonsustained VT)
    b. Amiodarone
        i. No better than ICD in reducing SCD as a lone agent; no mortality benefit
        ii. Can be used to treat symptomatic nonsustained VT if β-blockers not effective when ICD not indicated
        iii. Can be used in combination with β-blockers to decrease firing of ICD (defibrillator storm)
    c. Sotalol
        i. No mortality advantage
        ii. Can suppress VT and be used to decrease frequency of ICD firing
        iii. Greater proarrhythmic potential; avoid in patients with severely depressed LVEF or significant HF; renal dosing necessary

H. Treatment of Arrhythmias in Special Patient Populations
1. Heart failure
    a. Avoid class Ia and class Ic agents.
    b. Amiodarone and dofetilide (used for atrial arrhythmias only) have a neutral effect on mortality in patients with LV dysfunction after an MI.
    c. Dronedarone (used in atrial arrhythmias only) is contraindicated in patients with symptomatic HF with recent decompensation necessitating hospitalization or NYHA class IV symptoms; risk of death was doubled in these patients.
2. Acute MI
    a. Avoid class Ia and class Ic agents.
    b. CAST trial with class Ic agents (encainide, flecainide) showed greater mortality when used to treat post-MI non–life-threatening ventricular arrhythmias; avoid class Ic agents in patients with SHD.
    c. Class Ia medications: Increased mortality in MI survivors
    d. Amiodarone and dofetilide (used for atrial arrhythmias only) have a neutral effect on mortality in patients with LV dysfunction after an MI.

I. Drug-Induced Arrhythmias: Review all potential drug etiologies and treat appropriately.
1. Drug-induced QT prolongation
    a. Discontinue offending agent if QT prolongation is significant.
    b. Ensure proper renal and hepatic dosing adjustments.
    c. Review electrolyte abnormalities and thyroid function tests.
    d. Ensure that all electrolytes are maintained at critical concentrations: K^+ greater than 4–5 mEq/L and magnesium greater than 2 mg/dL.
    e. Ensure that all ECG parameters are within normal limits.
    f. Limitations to QTc calculations include consideration of QRS duration, ventricular conduction delays, ventricular pacemakers, arrhythmias, and QT correction based on ventricular rate.

2. Drug-induced bradycardia or atrioventricular block
   a. β-Blocker, CCB, digoxin
   b. Administer antidote, if appropriate (e.g., calcium for CCB toxicity).
3. Review for drug interactions. AADs have drug interactions that may cause significant outcomes.

Patient Cases

Questions 8 and 9 pertain to the following case.

A 68-year-old man is admitted after an episode of syncope, with a presyncopal syndrome of seeing black spots and dizziness before passing out. Telemetry monitor showed sustained VT for 45 seconds. His medical history includes HF NYHA class III, LVEF 30%, two MIs, hypertension for 20 years, LV hypertrophy, diabetes, and diabetic nephropathy. His medications include lisinopril 5 mg/day, furosemide 20 mg twice daily, metoprolol 25 mg twice daily, digoxin 0.125 mg/day, glipizide 5 mg/day, atorvastatin 40 mg, and aspirin 81 mg/day. His blood pressure is 120/75 mm Hg, with heart rate 80 beats/minute, BUN 30 mg/dL, and SCr 2.2 mg/dL.

8. Which is the best therapy to initiate for conversion of his sustained VT?
   A. Amiodarone 150 mg intravenously for 10 minutes, then 1 mg/minute for 6 hours, then 0.5 mg/minute.
   B. Sotalol 80 mg twice daily titrated to QTc of about 450 milliseconds.
   C. Dofetilide 500 mcg twice daily titrated to QTc of about 450 milliseconds.
   D. Procainamide 20 mg/minute, with a maximum of 17 mg/kg.

9. The patient presents to the ED 3 months after amiodarone maintenance initiation (he refused ICD placement) after a syncopal episode, during which he lost consciousness for 30 seconds, according to witnesses. He also has rapid heart rate episodes during which he feels dizzy and lightheaded. He feels very warm all the time (he wears shorts, even though it is winter), cannot sleep, and has lost 3 kg in weight. He received a diagnosis of hyperthyroidism caused by amiodarone therapy. On telemetry, he has runs of nonsustained VT. Which best predicts the duration of amiodarone-associated hyperthyroidism in this patient?
   A. 12 hours.
   B. 1 month.
   C. 6 months.
   D. 18 months.

10. A 64-year-old woman presents to the ED with the chief concern of palpitations. Her medical history includes hypertension controlled with a diuretic and an inferior-wall MI 6 months ago. She is pale and diaphoretic but can respond to commands. The patient's laboratory values are within normal limits. Her vital signs include blood pressure 95/70 mm Hg and heart rate 145 beats/minute; telemetry shows sustained VT. Despite chronic use of β-blocker therapy, the patient has developed sustained VT that is successfully terminated with lidocaine. Subsequent electrophysiologic testing reveals inducible VT, and sotalol 80 mg orally twice daily is prescribed. Two hours after the second dose, the patient's QTc is 520 milliseconds. Which regimen change would be most appropriate for this patient?
    A. Continue sotalol at 80 mg orally twice daily.
    B. Increase sotalol to 120 mg orally twice daily.
    C. Discontinue sotalol and initiate dofetilide 125 mcg orally twice daily.
    D. Discontinue sotalol and initiate amiodarone 400 mg orally three times daily.

IV. HYPERTENSIVE CRISES

A. Definitions
   1. Hypertensive emergency
      a. Severe elevations in blood pressure (usually greater than 180/120 mm Hg) with evidence of new or worsening target-organ damage
      b. Acute target-organ damage can include hypertensive encephalopathy, intracranial hemorrhage, acute ischemic stroke, or other acute neurologic deficit; UA or acute MI; acute LV failure with pulmonary edema; aortic dissection; retinopathy or papilledema; decreased urinary output or acute renal failure; eclampsia
      c. Actual blood pressure may not be as important as the rate of blood pressure rise.
      d. Requires immediate blood pressure lowering (not necessarily to normal ranges) to prevent or limit further target-organ damage
   2. Hypertensive urgency
      a. Situations associated with severe blood pressure elevation in otherwise stable patients without acute or impending change in target-organ damage or dysfunction
      b. Short-term risk is not as high; therefore, blood pressure reduction occurs over several days, not immediately.

B. Goals and Treatment
   1. Hypertensive emergency
      a. Goal is to minimize target-organ damage safely by rapid recognition of the problem and early initiation of appropriate antihypertensive treatment.
      b. Patients are usually admitted for intensive care unit care and close follow-up.
      c. Lower MAP by no more than 25% in the first hour; then reduce SBP to 160 mm Hg and diastolic blood pressure (DBP) to 100–110 mm Hg over next 2–6 hours; then to normal over next 24–48 hours
      d. Exceptions:
         i. Do not lower blood pressure in acute ischemic stroke unless greater than 220/120 mm Hg or greater than 185/110 mm Hg in thrombolysis candidates.
         ii. Lower SBP to less than 140 mm Hg in the first hour of treatment in severe preeclampsia or eclampsia and in pheochromocytoma with hypertensive crisis.
         iii. Lower SBP to less than 120 mm Hg and HR less than 60 beats/minute in the first hour of treatment in aortic dissection.
      e. Intravenous medications used commonly (Table 21)
      f. No randomized evidence to suggest one drug of choice because of small trial size, lack of long-term follow-up, and failure to report outcomes
      g. Two trials have shown that nicardipine is better than labetalol in achieving the short-term blood pressure target.
      h. Agents are chosen on the basis of drug pharmacology, pathophysiologic factors underlying the patient's hypertension, degree of progression of target-organ damage, desirable rate of blood pressure decline, and presence of patient characteristics (Tables 21 and 22).
      i. No randomized evidence exists comparing different strategies to reduce blood pressure, except in patients with intracranial hemorrhage.
      j. No randomized evidence suggests how rapidly to reduce blood pressure.
      k. Clinical experience indicates that excessive reductions in blood pressure can cause renal, cerebral, or coronary ischemia and should be avoided.

2. Hypertensive urgency
   a. Treated by reinstitution or intensification of antihypertensive drug therapy
   b. No indication for referral to the ED, immediate reduction in blood pressure in the ED, or hospitalization
   c. No proven benefit exists from rapid reductions in blood pressure.
   d. Choice of agent used in this setting varies, and in many cases, adjusting chronic oral therapy (increasing doses), reinitiating therapy in the nonadherent, or adding a new agent (i.e., diuretic) to long-term therapy is appropriate. Use of intravenous agents has been associated with adverse events and prolonged hospitalization
   e. All patients with hypertensive urgency should be reevaluated within 7 days (preferably after 1–3 days).

C. Treatment Options (Table 21)

Table 21. Commonly Used IV Drugs for Hypertensive Emergencies

Drug (onset, duration)	IV Dose	Comments/AEs
Vasodilators		
Sodium nitroprusside (Nipride) (immediate, 2–3 min)	0.3–0.5 mcg/kg/min, increase in increments of 0.5 mcg/kg/min to achieve BP target; max 10 mcg/kg/min; for infusion rates ≥ 4–10 mcg/kg/min or duration > 30 min	Intra-arterial BP monitoring recommended to prevent "overshoot"; lower doses required in older adult patients; tachyphylaxis may occur with extended use AEs: Cyanide or thiocyanate toxicity with prolonged use can result in irreversible neurologic changes and cardiac arrest, nausea, vomiting, methemoglobinemia CIs: Renal, hepatic failure Caution: Elevated ICP, may cause coronary steal in setting of coronary ischemia
Nitroglycerin (2–5 min, 5–10 min)	5–10 mcg/min, increase in increments of 5 mcg/min every 3–5 min to a max 200 mcg/min	Use only in patients with ACS and/or acute pulmonary edema; do not use in volume-depleted patients or in patients with right ventricular infarction AEs: Headache, nausea, vomiting, tachyphylaxis
Hydralazine (Apresoline) (10 min, 1–4 hr)	5–10 mg by slow IV infusion every 4–6 hr (NTE initial 20 mg/dose)	BP begins to decrease within 10–30 min, and lasts 2–4 hr; unpredictability of response and prolonged duration of action make hydralazine less desirable first agent AEs: Reflex tachycardia, headache, flushing Caution: Angina or MI, elevated ICP, aortic dissection
Enalaprilat (Vasotec) (within 30 min, 12–24 hr)	0.625–1.25 mg over 5 min; doses can be increased up to max 5 mg every 6 hr	Should not be used in acute MI; mainly useful in hypertensive emergencies associated with high plasma renin activity; dose not easily adjusted; relatively slow onset (15 min), long half-life, and unpredictability of BP response AEs: Renal insufficiency or failure, hyperkalemia CIs: Pregnancy, bilateral renal artery stenosis, angioedema

Table 21. Commonly Used IV Drugs for Hypertensive Emergencies *(Cont'd)*

Drug (onset, duration)	IV Dose	Comments/AEs
Vasodilators		
Fenoldopam (Corlopam) (< 5 min, 30 min)	0.1–0.3 mcg/kg/min, increased by 0.05–0.1 mcg/kg/min every 15 min to a max of 1.6 mcg/kg/min	Contraindicated in patients at risk of increased intraocular pressure (glaucoma) or ICP and those with sulfite allergy AEs: Headache, flushing, tachycardia, cerebral ischemia
Nicardipine (Cardene) (1–5 min, 15–30 min; up to 4 hr if prolonged infusion)	5 mg/hr, increased by 2.5 mg/hr every –15 min to a max 15 mg/hr	Contraindicated in advanced aortic stenosis; no dose adjustment needed for older patients AEs: Reflex tachycardia, nausea, vomiting, headache, flushing Caution: Angina or MI, acute HF
Clevidipine (Cleviprex) (2–4 min, 5–15 min)	1–2 mg/hr, doubling every 90 s until BP approaches target, then increasing by less than double every 5–10 min; max 32 mg/hr; max duration 72 hr	Patients with renal failure and hepatic failure and older adults not specifically studied – use low-end range for older adults; contraindicated in soy or egg product allergy, severe aortic stenosis, defective lipid metabolism (e.g., pathologic hyperlipidemia, lipoid nephrosis, or acute pancreatitis) Caution: HF, concomitant β-blocker use, reflex tachycardia, rebound HTN
Adrenergic Inhibitors		
Esmolol (Brevibloc) (1–2 min, 10–30 min)	LD 500–1000 mcg/kg IVB over 1 min, then a 50-mcg/kg/min infusion; titrated every 5 min in 50-mcg/kg/min increments as needed to a max 200 mcg/kg/min	Contraindicated in patients with concurrent β-blocker therapy, bradycardia, or decompensated HF AEs: Bronchospasm, HF exacerbation, bradycardia or heart block Caution: May worsen acute HF, asthma (higher doses may block β2-receptors and affect lung function in reactive airway disease), heart block
Labetalol (Normodyne, Trandate) (5–10 min, 3–6 hr)	20–80 mg every 15 min or initial 0.3–1 mg/kg dose (max 20 mg) slow IV injection every 10 min or 0.4–1.0 mg/kg/hr infusion up to max 3 mg/kg/hr	Contraindicated in reactive airway disease or chronic obstructive pulmonary disease; especially useful in hyperadrenergic syndromes; may worsen HF and should not be given in patients with second- or third-degree heart block or bradycardia Caution: Prolonged hypotension may occur with overtreatment
Phentolamine (2 min, 15–30 min)	IVB dose 1–5 mg; additional bolus doses every 10 min as needed	Used in hypertensive emergencies induced by catecholamine excess (pheochromocytoma, monamine oxidase inhibitors interactions with food and/or drugs, cocaine toxicity, amphetamine overdose, or clonidine withdrawal)

AE = adverse effect; CI = contraindication; ICP = intracranial pressure.

Table 22. Agents Preferred for Hypertensive Crises According to Comorbidities

Comorbidity	Preferred Agents	Comments
Acute aortic dissection	Labetalol, esmolol	Requires rapid lowering of SBP to ≤ 120 mm Hg within 20 min; heart rate target <60 bpm β-blocker should be given before vasodilator (nicardipine or NTP) if needed for BP control or to prevent reflex tachycardia or inotropic effect
Acute coronary syndromes	Esmolol or NTG (preferred), labetalol, nicardipine	Nitrates given in the presence of PDE-5 inhibitors may induce profound hypotension; contraindications to β-blockers include moderate to severe LV failure with pulmonary edema, right ventricular infarction, bradycardia (< 60 beats/min), hypotension (SBP < 100 mm Hg), poor peripheral perfusion, second- or third-degree heart block, and reactive airway disease
Acute pulmonary edema	Clevidipine, NTG, NTP	β-Blockers contraindicated; NTG preferred for ADHF
Acute renal failure	Clevidipine, fenoldopam, nicardipine	
Eclampsia or preeclampsia	Labetalol, nicardipine, hydralazine (second line)	Requires rapid BP lowering to < 140 mm Hg within first hour; ACE inhibitor, ARBs, renin inhibitors, and NTP contraindicated
Perioperative HTN (BP ≥ 160/90 mm Hg or SBP elevation > 20% of the preoperative value that persists > 15 min)	Clevidipine, esmolol, nicardipine, NTG	Intraoperative HTN is most common during anesthesia induction and airway manipulation
Acute sympathetic discharge or catecholamine excess states (e.g., pheochromocytoma, post-carotid endarterectomy status)	Clevidipine, nicardipine, phentolamine (Note: Avoid unopposed β-blockade)	Requires rapid lowering of BP
Acute intracranial hemorrhage	IV continuous infusion Most studied agents in this setting are nicardipine, clevidipine, labetalol	Lower BP in those who present with SBP > 220 mm Hg with continuous IV infusion and close BP monitoring; immediate lowering of SBP < 140 mm Hg is not of benefit and may be harmful. Avoiding medications that can increase ICP and worsen cerebral ischemia (hydralazine, NTG, and NTP)
Acute ischemic stroke	No preference of agent	Early initiation or resumption of antihypertensive treatment indicated only in (1) patients treated with tissue-type plasminogen activator to BP < 185/110 mm Hg and (2) patients with SBP > 220 mm Hg or DBP > 120 mm Hg; cerebral autoregulation in the ischemic penumbra of the stroke is grossly abnormal and rapid reduction of BP can be harmful; reinitiate antihypertensive therapies in those with preexisting HTN after neurologic stability

ARB = angiotensin receptor blocker; BP = blood pressure; NTG = nitroglycerine; NTP = nitroprusside.

Patient Cases

11. A 68-year-old man with a history of stage 5 chronic kidney disease receiving hemodialysis, hypertension, CAD post-MI, HFrEF, and gastroesophageal reflux disease presents with acute-onset shortness of breath and chest pain. After his recent dialysis, he was nonadherent to medical therapy for 2 days and noticed he had gained 2 kg in 24 hours. His baseline orthopnea worsened to sleeping sitting up in a chair for the 2 nights before admission. He admits smoking cocaine within the past 24 hours and developed acute-onset chest tightness with diaphoresis and nausea, and his pain was 7/10. He went to the ED, where his blood pressure was 250/120 mm Hg. He had crackles halfway up his lungs on examination, and chest radiography detected bilateral fluffy infiltrates with prominent vessel cephalization. His ECG revealed sinus tachycardia, heart rate 122 beats/minute, and ST-segment depressions in leads 2, 3, and aVF. He was admitted for a hypertensive emergency. Laboratory results are as follows: BUN 48 mg/dL, SCr 11.4 mg/dL, BNP 2350 pg/mL, troponin T 1.5 ng/L (less than 0.1 mcg/L), creatine kinase 227 units/L, and creatine kinase-MB 22 units/L. Which medication is best for this patient's hypertensive emergency?

    A. Intravenous nitroglycerin 5 mcg/minute titrated to a 25% reduction in MAP.

    B. Labetalol 2 mcg/minute titrated to a 50% reduction in MAP.

    C. Sodium nitroprusside 0.25 mcg/kg/minute titrated to a 25% reduction in MAP.

    D. Clonidine 0.1 mg orally every 2 hours as needed for a 50% reduction in MAP.

12. A 56-year-old white woman with a long history of hypertension because of nonadherence and recently diagnosed HF (ejection fraction 35%) presents to the local ED with blood pressure 210/120 mm Hg and heart rate 105 beats/minute. She states that she felt a little lightheaded but that she now feels okay. She ran out of her blood pressure medications (including hydrochlorothiazide, carvedilol, and lisinopril) 3 days ago. Her current laboratory values are within normal limits. Which medication is best for this patient?

    A. Sodium nitroprusside 0.25 mcg/kg/minute titrated to a 25% reduction in MAP.

    B. Labetalol 80 mg intravenously; repeat until blood pressure is less than 120/80 mm Hg.

    C. Resumption of home medications; refer for follow-up within 2 days.

    D. Resumption of home medications; initiate amlodipine 10 mg daily; refer for follow-up in 1 week.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: A

This patient's atypical symptoms, ST-segment depression on ECG, and positive biomarkers for myocardial necrosis suggest NSTE-ACS. She has at least three risk factors for CAD, a history of CAD (prior MI), and positive troponins, which place her at high risk of future events. In such high-risk patients, an early invasive strategy (as in Answers A and B) is used to determine whether occluded or partly occluded arteries exist, which ones can be intervened on, and whether to make an intervention. An ischemia-guided approach, also called "medical management," as in Answers C and D, would not be preferred because of this patient's risk category (i.e., positive troponins). Dual antiplatelet therapy (aspirin plus a $P2Y_{12}$ inhibitor) is indicated for an early invasive strategy in managing an NSTE-ACS. In patients undergoing PCI, clopidogrel, prasugrel, or ticagrelor is appropriate (Answer A is correct). After an initial bolus of 60 units/kg and an infusion of 12 units/kg/hour (Answer A is correct; Answer D is incorrect), UFH can be titrated to an aPTT of 50–70 seconds. Aspirin alone without a $P2Y_{12}$ agent, as in Answer B, would not provide adequate antiplatelet therapy. Furthermore, enoxaparin would need to be dosed with a 30-mg intravenous bolus before initiating twice-daily subcutaneous dosing because this patient has positive troponins. Glycoprotein IIb/IIIa inhibitors, as in Answer C, can be useful in high-risk patients, typically those with positive troponins; however, their benefit has been shown mainly when UFH, not low-molecular-weight heparin, is given as the anticoagulant.

2. Answer: C

Of importance, this patient case occurs in the context of elective stent placement, not after ACS. In the non-ACS setting, the duration of DAPT is determined by the type of stent placed (bare metal stent vs. drug-eluting stent). After elective drug-eluting stent placement, DAPT is recommended for at least 6 months because the risk of in-stent thrombosis is highest during this time (Answer C is correct). The recommendation is for at least 1 month after bare metal stent placement because endothelialization of the stent usually occurs early, typically within 1 month after stenting (Answer A is incorrect). Bleeding risk may be a reason to consider earlier termination (after at least 1 month) of DAPT after bare metal stent placement. Although European guidelines consider 3 months of DAPT after drug-eluting stent placement appropriate, the recommended minimum according to the U.S. guidelines is 6 months (Answer B is incorrect). Twelve months of therapy is recommended after ACS (Answer D is incorrect).

3. Answer: D

Because the patient presents to a hospital that can do a primary PCI with stent implantation, this is the preferred reperfusion strategy (Answers B and C are incorrect). Answer A is incorrect because an anticoagulant agent must be administered in addition to antiplatelet therapy. Reperfusion with fibrinolytic therapy (Answers B and C) would only be considered if PCI were expected to be delayed by more than 120 minutes. In addition, Answer C is incorrect because bivalirudin has not been studied with lytic therapy. Answer D – reperfusion with primary PCI, DAPT with aspirin and prasugrel, and dosing of bivalirudin as an anticoagulant strategy – is correct.

4. Answer: C

Unlike the patient in case 3, this patient presents with a STEMI to a rural community hospital where the nearest hospital with catheterization laboratory facilities is more than 120 minutes away (i.e., lytics are indicated). He presents within the window for fibrinolytic therapy consideration (less than 6 hours after chest pain onset) and has no obvious contraindications. Because he is still having ischemic chest pain and ST-segment elevation, he should benefit from reperfusion therapy. He is experiencing bradycardia, which could indicate an occlusion above the area perfusing his sinoatrial or atrioventricular nodes. Enoxaparin is a treatment option for anticoagulant therapy given in conjunction with fibrinolytics, but the patient is at higher risk of bleeding from impaired enoxaparin clearance and needs a dosage adjustment. Furthermore, he is older than 75, beyond the age at which the intravenous bolus should be given, and the alteplase dosing is incomplete (Answer A is incorrect). Simply treating this patient conservatively with UFH alone in the setting of ongoing chest pain, shortness of breath, and pulmonary edema is not optimal (Answer B is incorrect). Diagnostic catheterization and possible PCI to determine whether an artery can be reperfused may be desirable but is complicated because the patient's SCr is elevated (2.5 mg/dL), and he is in a rural hospital, where he cannot be assessed

quickly enough (within 90–120 minutes) (Answer D is incorrect). Because of the shorter half-life and ease of administration of tenecteplase, tenecteplase may be preferable to alteplase. Clearance of UFH with tenecteplase is not as altered as with enoxaparin, and it would be a more appropriate therapy than enoxaparin in combination with a thrombolytic (Answer C is correct).

5. Answer: C

This patient, who has ADHF, is receiving a β-blocker. Although long-term β-blockers can improve HF symptoms and reduce mortality, they can also worsen symptoms in the short term. It is recommended to keep the maintenance β-blocker therapy at the same or at a slightly lower dose compared with the outpatient therapy in patients with ADHF; increasing the β-blocker dose before reaching euvolemia might acutely worsen his clinical picture (Answer A is incorrect). In patients admitted with volume overload without substantial signs of reduced CO, it is reasonable to try intravenous loop diuretics initially (Answer C is correct). As gut edema increases, oral loop diuretics (notably furosemide) become less effective because of decreased absorption. Sodium nitroprusside could be useful if signs and symptoms of hypoperfusion were present. Because this patient presents mainly with warm and wet symptoms, diuretics would be first-line (Answer B is incorrect). Milrinone is an inotropic drug. Because of their adverse effects, inotropes are recommended in cold and wet exacerbations only after vasodilatory medications have failed (Answer D is incorrect).

6. Answer: A

Intravenous vasodilators such as nitroglycerin (Answer A) and sodium nitroprusside (Answer B) are reasonable if intravenous diuretics fail and the patient progresses to acute pulmonary edema. Both agents rapidly cause venous vasodilation and reduce pulmonary filling pressures, which can relieve acute shortness of breath. Answer A, nitroglycerin, is optimal for this patient, given his declining renal function and the concern for increased risk of thiocyanate toxicity with sodium nitroprusside in this setting (Answer B is incorrect). Dobutamine is typically used in states of low CO decompensation and is counteracted by concomitant β-blocker therapy, making it a poor choice in patients receiving β-blockers (Answer C is incorrect). Although milrinone is a more acceptable inotropic agent in a patient receiving β-blockers, the dosing strategy is inappropriate as an initial dose (Answer D is incorrect). Finally, inotropes are generally reserved for patients when other therapies have failed.

7. Answer: A

Signs of a decreased CO state in HF (e.g., increased SCr, decreased mental status, cool extremities) suggest a cold and wet state, and adjunctive therapy is indicated. Positive inotropic agents such as milrinone will increase CO to maintain perfusion to vital organs. Milrinone will also vasodilate the peripheral vessels to unload the heart (lower SVR). Although dobutamine would be a potential choice in this patient, it is not recommended in patients receiving β-blockers, and the initial starting dose is too aggressive (Answer B is incorrect). Although this patient has low blood pressure, his elevated SVR suggests that he will tolerate the vasodilatory effects of milrinone as long as it is appropriately renally adjusted for worsening renal dysfunction (Answer A is correct). Nitroprusside would be relatively contraindicated in patients with an SBP less than 100 mm Hg and is absolutely contraindicated in patients with an SBP less than 90 mm Hg (Answer C is incorrect). Phenylephrine has no positive beta effects; therefore, it will not augment contractility. In addition, it will cause vasoconstriction through alpha stimulation, which will further increase SVR and probably worsen CO (Answer D is incorrect). Vasoconstrictors are reserved for patients in cardiogenic shock.

8. Answer: A

Treatment options for sustained VT depend on concomitant disease states, particularly LVEF (40% cutoff). In a patient with LV dysfunction, class I agents such as procainamide are contraindicated (Answer D is incorrect). In a patient whose CrCl is less than 60 mL/minute, sotalol requires a considerable dose reduction to avoid an excess risk of torsades de pointes. Sotalol is not an effective cardioversion drug but is more useful for preventing future episodes of arrhythmias (maintaining sinus rhythm) once sinus rhythm is achieved (Answer B is incorrect). Dofetilide is indicated only for AF, not for ventricular arrhythmias; similarly, cardioversion rates with dofetilide are low (Answer C is incorrect). Amiodarone is first-line therapy for sustained VT in patients with severe renal insufficiency, HF, and SHD (Answer A is correct).

9. Answer: C

With the prolonged half-life of amiodarone and extensive fat tissue volume of distribution, hyperthyroid adverse effects would be expected to last for 3–5 half-lives of the drug, which is 5–8 months (Answer C is correct; Answer A is incorrect). Although therapeutic concentrations may decrease substantially by then, 1 month is too soon for the effects to subside (Answer B is incorrect). Although some iodine and amiodarone molecules will probably remain absorbed in fat stores for years, if not for life, therapeutic concentrations should not exist for longer than what is predicted by the half-life (Answer D is incorrect).

10. Answer: D

This patient is having QT prolongation with sotalol, placing her at an elevated risk of developing life-threatening torsades de pointes. Sotalol should be discontinued immediately (Answers A and B are incorrect). Given the QT prolongation that occurred with sotalol, the same will probably occur with dofetilide (Answer C is incorrect). Amiodarone is associated with minimal risk of torsades de pointes and therefore would be an appropriate alternative agent to prevent ventricular arrhythmias (Answer D is correct).

11. Answer: A

Hypertensive emergency should be treated immediately by no more than a 25% reduction in MAP over the first hour, followed by a further reduction to a blood pressure of 160/100 mm Hg over the next 2–6 hours. The patient's comorbidities guide the optimal therapy. His dialysis and SCr of 11.4 mg/dL are contraindications to sodium nitroprusside (Answer C is incorrect) because of possible thiocyanate toxicity. Labetalol (and β-blockers in general) is controversial in patients who have taken cocaine, but its nonselective nature makes it an option; however, this patient appears to have decompensated HF, and a reduction of 50% initially is too rapid a decrease in blood pressure for safety (Answer B is incorrect). Clonidine is not appropriate for a hypertensive emergency because its oral form is difficult to titrate and can lead to precipitous drops in blood pressure beyond the goal 25% reduction and possibly stroke or worsening MI (Answer D is incorrect). Nitroglycerin is optimal, considering the patient's lack of contraindications to this therapy and his evolving MI and symptoms of HF (Answer A is correct).

12. Answer: C

In an asymptomatic hypertensive crisis (without acute target-organ damage), giving intravenous medications, as in Answers A and B, and admitting the patient to the hospital are unnecessary (Answers A and B are incorrect). This patient is likely presenting because of recent nonadherence. Resuming her home medications (Answer C is correct) at this time would be most appropriate, with a close follow-up to ensure that her prescribed regimen is working. Adding a fourth agent (Answer D is incorrect) at this time is unnecessary, considering that her disease could be controlled on her current drug regimen if she were adherent. Follow-up should occur within the first few days, rather than waiting 1 week.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: C

This patient's chest pain, ST-segment depression on ECG, and positive biomarkers for myocardial necrosis suggest NSTE-ACS. Because of his presentation characteristics, he is at a high enough risk to warrant cardiac catheterization (invasive strategy). This invasive strategy is used to determine whether occluded or partly occluded epicardial arteries exist, which ones can be intervened on, and whether to do PCI (percutaneous transluminal coronary angioplasty with or without stenting). Initial therapy for ACS usually consists of morphine, oxygen, nitroglycerin, and aspirin, but only aspirin has been shown to reduce mortality from these initial treatments. Aspirin should be given as soon as possible after hospital presentation and continued indefinitely, if tolerated. According to clinical trials, guidelines, and experience, an initial dose of 162–325 mg is recommended (Answers B and D are not the best choices of dosing for an acute episode). Aspirin, together with a $P2Y_{12}$ receptor antagonist, is indicated for an early invasive strategy in the management of UA/NSTEMI, improving outcomes. The 2014 NSTE-ACS guidelines give a class I recommendation for clopidogrel, ticagrelor, and prasugrel in ACS for patients undergoing PCI. The choice of which $P2Y_{12}$ receptor antagonist to use in the ACS setting depends on patient presentation, contraindications, and whether PCI is involved; in this case, any of the three $P2Y_{12}$ antagonists would be appropriate. The anticoagulation strategy treatment for ACS generally includes one anticoagulant (UFH, low-molecular-weight heparin, fondaparinux, or bivalirudin). When UFH is chosen as an anticoagulant strategy, the dose used for ACS is a 60-unit/kg bolus and a 12-unit/kg/hour infusion (Answer A is incorrect). Regarding dosing, bivalirudin (Answer D) would be an appropriate anticoagulation strategy; however, the initial aspirin dose should be higher, and a nitroglycerin drip would not be the best choice, given his right-sided MI (low blood pressure, low heart rate). Answer A is reasonable in patients without contraindications when hypertension or ongoing ischemia is a concern; however, initiating oral therapy within 24 hours is preferred in most patients as long as they have no signs of HF, evidence of low output state, increased risk of cardiogenic shock, or other contraindications to β-blockade. β-Blockers should initially be avoided in this patient, given his blood pressure and decreased baseline heart rate. An intravenous ACE inhibitor (Answer B) should not be given to patients within the first 24 hours of ACS because of the increased risk of hypotension. Answer C includes DAPT and an appropriate anticoagulant dose (Answer C is correct).

2. Answer: A

The NSTE-ACS guidelines recommend the use of one anticoagulant during an acute event. Enoxaparin, UFH, and bivalirudin are all recommended as class I agents for the invasive management of NSTE-ACS. However, fondaparinux (Answer C) is not optimal because of the increased risk of catheter-related thrombosis associated with its use in the catheterization laboratory. The NSTE-ACS guidelines advise the use of an additional anticoagulant with class IIa activity (heparin or bivalirudin) if fondaparinux was an initial anticoagulant when the patient underwent intervention, whereas the PCI guidelines give fondaparinux a class III or harmful recommendation. Of the remaining three options, UFH (Answer A) is preferred because of its dosage and rapid clearance regardless of renal function. The UFH bolus should be limited to 4000 units, and the initial infusion should be limited to 1000 units/hour. Both enoxaparin (Answer B) and bivalirudin (Answer D) would be appropriate but would need to be dose adjusted, given this patient's CrCl of less than 30 mL/minute. However, the doses in Answers B and D would be appropriate for patients with a normal CrCl.

3. Answer: B

An anticoagulant is required for PCI. Options include UFH, bivalirudin, and enoxaparin. Because this patient had a significantly low Plt with his most recent heparin exposure and was confirmed to have HIT, using any of the GP IIb/IIIa inhibitors (Answer A) would be unwise for ACS treatment because these agents are usually combined with UFH. Furthermore, GP IIb/IIIa inhibitors are antiplatelets, and the patient will still need an additional agent with anticoagulant activity. Thrombolytic therapy is not recommended for NSTE-ACS and would be inappropriate in this patient (Answer D is incorrect). Answer C is incorrect because enoxaparin carries a 10% risk of cross-reactivity if HIT is suspected. Bivalirudin (Answer B), a direct thrombin inhibitor, would be the treatment of choice in patients with HIT undergoing PCI.

4. Answer: D

β-Blocker therapy can cause HF decompensation, particularly when the β-blocker is titrated too quickly or initiated in patients who are not euvolemic. Although administering β-blockers within the first 24 hours is beneficial in STEMI, this patient has several risk factors that would be considered contraindications to initial β-blockade. This patient's clinical condition suggests he is not euvolemic, and aggressive diuresis should be tried before a β-blocker is initiated for him. In addition, intravenous β-blocker therapy (Answer B) would place him at an even greater risk of cardiogenic shock. Answers A and C are inappropriate because the doses are fairly aggressive for a patient with marginal blood pressure at this time. Answer D is correct; however, before discharge, this patient should be reevaluated for the initiation of low-dose β-blocker therapy.

5. Answer: B

Dual antiplatelet therapy is recommended for at least 12 months in patients presenting with ACS. Early discontinuation of DAPT is reasonable when the risk of morbidity exceeds the expected benefit (class IIa), as in the case of bleeding. Answers C and D do not represent the minimum time interval, given that the patient has no known risk of bleeding. Prasugrel (Answer B) would be preferable to clopidogrel (Answer A) in this scenario because it would be faster in onset; clopidogrel would take about 6 hours for maximal platelet inhibition after a 300-mg LD. Subgroup analysis of a Triton-TIMI 38 comparing the effectiveness of prasugrel and clopidogrel showed the superiority of prasugrel, especially for patients presenting with a STEMI (Answer B is correct).

6. Answer: C

This patient is well perfused and can be classified in Forrester hemodynamic subset II (warm and wet). Because the patient has pulmonary congestion (shortness of breath, dyspnea at rest), intravenous diuretics are first-line therapy. Nitroglycerin (Answer C) is best in this setting because vasodilatory agents can be used in conjunction with intravenous diuretics to improve acute pulmonary edema. When adjunctive therapy is needed in addition to loop diuretics, intravenous vasodilators should be considered over inotropic agents when blood pressure is adequate. Dobutamine (Answer A) and milrinone (Answer B) primarily increase CO, which is not a problem in warm and wet exacerbations. In addition, the adverse effects of these agents (increased mortality, proarrhythmia) limit their use. Intravenous metoprolol (Answer D) should be used extremely cautiously because of its negative inotropic effects and because this patient is not in a euvolemic state.

7. Answer: D

This patient has a depressed LVEF less than 40%; therefore, her AAD therapy options are limited. Procainamide (Answer A) is indicated only in secondary prevention of sustained VT in patients with a normal LVEF greater than 40%; if given to this patient, it could worsen her HF. Metoprolol (Answer B) is indicated for treating patients with asymptomatic nonsustained VT and SVT associated with CAD. This patient had an episode of sustained VT; therefore, therapy beyond β-blockade is warranted. Her QTc interval is not prolonged at 380 milliseconds, and her serum magnesium concentration is within normal limits; thus, she does not need intravenous magnesium therapy (Answer C). Amiodarone (Answer D) is first line for patients without contraindications because of its efficacy and safety in patients with an LVEF less than 40%.

8. Answer: B

This patient has target-organ damage from poorly controlled hypertension in the form of retinal hemorrhaging. Fenoldopam is contraindicated for treating hypertensive emergencies in the setting of glaucoma (Answer A is incorrect). Nicardipine is appropriate for this patient, given the details of this case (Answer B is correct). Although labetalol is effective for treating hypertensive emergency, this patient has a history of asthma and a low heart rate, making labetalol a less-than-ideal option for treating her symptoms (Answer C is incorrect). The antihypertensive effects of enalaprilat depend on a patient's renin activity, which is unknown in this case. Therefore, the blood pressure–reducing effects may be more difficult to control than when using a drug having a more consistent effect in individuals. In addition, the bolus nature of the drug is not ideal for tightly controlling blood pressure with no more than a 25% reduction in MAP. Continuous infusion drugs are preferable for easier titration to effect in a hypertensive emergency (Answer D is incorrect).

9. Answer: C

The Cardiac Arrest Study Hamburg trial compared ICD with AAD in survivors of cardiac arrest for secondary prevention of SCD. The propafenone (Answer A) study

arm was discontinued early because of its significantly (61%) higher mortality rate compared with the ICD arm (Answer A is incorrect). Although this trial had a small sample size that prevented a statistically significant difference in total mortality in ICD-treated patients versus patients treated with either amiodarone or metoprolol, the incidence of sudden death was significantly lower in patients with an ICD (Answer C is correct; 33% vs. 13%; p=0.005). The Antiarrhythmics Versus Implantable Defibrillators trial also evaluated ICD implantation versus AAD therapy (primarily amiodarone) in survivors of SCD. Patients with ICDs had a significantly higher rate of survival than did those treated with drug therapy (89% vs. 82%; $p<0.02$), making Answer C preferable to all the other options (Answers B and D are incorrect).

10. Answer: C

The number needed to treat can be calculated as 1/absolute risk reduction. Because the absolute risk reduction in mortality at 60 months was 7.2% with ICD versus placebo, 1/0.072 would be used to calculate the number of patients needed to treat to prevent one death during this time. About 14 patients (Answer C) would need to be treated with ICD to prevent one death in 60 months versus placebo. Other calculations in this fashion, including relative risk reduction and 100% minus the absolute or relative risk reduction, provide no useful information for interpreting the trial results and yield an incorrect number of patients (Answers A, B, and D are incorrect).

Chronic Care in Cardiology

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Learning Objectives

1. Recommend patient-specific guideline-directed medical pharmacologic therapy for the management of chronic heart failure.
2. Develop an evidence-based pharmacologic regimen and monitoring plan for patients with atrial fibrillation.
3. Develop an optimal pharmacologic management plan for a patient with hypertension according to practice guidelines and clinical trial evidence.
4. Design an appropriate dyslipidemia regimen based on a patient's atherosclerotic cardiovascular disease (ASCVD) risk.
5. Determine the appropriate pharmacologic therapy for patients with chronic coronary disease.

Abbreviations in This Chapter

ACC/AHA	American College of Cardiology/ American Heart Association
ACCP	American College of Chest Physicians
ACE	Angiotensin-converting enzyme
ACS	Acute coronary syndrome
AF	Atrial fibrillation
ARB	Angiotensin II receptor blocker
ARNI	Angiotensin receptor-neprilysin inhibitor
ASCVD	Atherosclerotic cardiovascular disease
AV	Atrioventricular
BNP	Brain natriuretic peptide
BP	Blood pressure
CCB	Calcium channel blocker
CCD	Chronic coronary disease
CK	Creatine kinase
CKD	Chronic kidney disease
CO	Cardiac output
CV	Cardiovascular
CYP	Cytochrome P450
DAPT	Dual antiplatelet therapy
DASH	Dietary Approaches to Stop Hypertension
DBP	Diastolic blood pressure
DES	Drug-eluting stent
DHA	Docosahexaenoic acid
DHP	Dihydropyridine
DOAC	Direct oral anticoagulant
ECG	Electrocardiogram
EPA	Eicosapentaenoic acid
GERD	Gastroesophageal reflux disease
GI	Gastrointestinal
HDL-C	High-density lipoprotein-cholesterol
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HFrecEF	Heart failure with recovered ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HFSA	Heart Failure Society of America
HR	Heart rate
HRS	Heart Rhythm Society
HTN	Hypertension
INR	International normalized ratio
K	Potassium
LDL-C	Low-density lipoprotein-cholesterol
LFTs	Liver function tests
LVEF	Left ventricular ejection fraction
mAb	Monoclonal antibody
MACE	Major adverse cardiovascular events
MI	Myocardial infarction
MRA	Mineralocorticoid receptor antagonist
Na	Sodium
NSAID	Nonsteroidal anti-inflammatory drug
NSR	Normal sinus rhythm
NYHA	New York Heart Association
P-gp	P-glycoprotein
PAD	Peripheral arterial disease
PCE	Pooled Cohort Equation
PCI	Percutaneous coronary intervention
PCSK9	Proprotein convertase subtilisin/kexin type 9 serine protease
PUFA	Polyunsaturated fatty acid
REMS	Risk Evaluation and Mitigation Strategy
SA	Sinoatrial
SAPT	Single antiplatelet therapy
SBP	Systolic blood pressure
SCr	Serum creatinine
SGLT2	Sodium-glucose cotransporter 2
SR	Sinus rhythm
SVR	Systemic vascular resistance
TC	Total cholesterol
TEE	Transesophageal echocardiogram
TG	Triglycerides
TIA	Transient ischemic attack

Self-Assessment Questions

Answers and explanations to these questions can be found at the end of this chapter.

1. R.S., a 58-year-old woman with a history of hypertension (HTN), chronic coronary disease (CCD), myocardial infarction (MI) 4 months ago, and dyslipidemia, presents to the clinic for a follow-up. She has no worsening signs or symptoms of dyspnea or edema compared with her baseline. An echocardiogram reveals a left ventricular ejection fraction (LVEF) of 35%. She is in New York Heart Association (NYHA) class III. Her medications include aspirin 81 mg/day, metoprolol succinate 150 mg/day, and atorvastatin 40 mg/day at night. Her vital signs include blood pressure (BP) 138/80 mm Hg and heart rate (HR) 58 beats/minute. Her lungs are clear, and laboratory results are within normal limits. Given her history and physical examination, what is the most appropriate modification to R.S.'s current drug therapy?
   A. Continue current therapy.
   B. Initiate digoxin 0.125 mg/day.
   C. Initiate vericiguat 2.5 mg/day.
   D. Initiate sacubitril 24 mg/valsartan 26 mg twice daily.

2. J.O. is a 64-year-old woman with NYHA class II nonischemic dilated cardiomyopathy (LVEF of 30%). She presents to the heart failure (HF) clinic for a follow-up. She is euvolemic. Her medications include enalapril 10 mg twice daily, furosemide 40 mg twice daily, and potassium chloride 20 mEq twice daily. Her vital signs include BP 130/88 mm Hg and HR 78 beats/minute. Her laboratory results are within normal limits. What is the best way to manage J.O.'s HF?
   A. Continue current regimen.
   B. Increase enalapril to 20 mg twice daily.
   C. Initiate carvedilol 3.125 mg twice daily.
   D. Initiate digoxin 0.125 mg/day.

3. J.M. is a 65-year-old woman with a history of HTN who presents to her primary care physician with shortness of breath and markedly decreased exercise tolerance. An echocardiogram reveals an LVEF of 65%, with diastolic dysfunction. J.M. currently takes losartan 150 mg/day for HTN. Her vital signs include BP 134/84 mm Hg and HR 68 beats/minute. Her lung fields are clear to auscultation, and there is no evidence of systemic congestion. Her laboratory results include SCr 1.1 mg/dL and K 5.1 mEq/L. Which is the best change to make to J.M.'s pharmacologic regimen today?
   A. Add metoprolol succinate 50 mg/day.
   B. Initiate furosemide 40 mg/day.
   C. Add spironolactone 25 mg/day.
   D. Add empagliflozin 10 mg/day.

4. B.W. is a 78-year-old man with a history of HTN, peripheral arterial disease (PAD), gastroesophageal reflux disease, and asymptomatic atrial fibrillation (AF) for the past month. His therapy includes aspirin 325 mg/day, lansoprazole 30 mg every night, atenolol 50 mg/day, lisinopril 10 mg/day, and atorvastatin 20 mg/day. His vital signs include BP 132/72 mm Hg and HR 68 beats/minute. Which is the best therapy for B.W. at this time?
   A. Add diltiazem and rivaroxaban.
   B. Add digoxin and increase lisinopril to 20 mg/day.
   C. Discontinue atorvastatin and add warfarin.
   D. Add apixaban and decrease aspirin to 81 mg/day.

5. Z.G. is a 61-year-old man with AF, HTN, and dyslipidemia. His medications include digoxin 0.125 mg/day, warfarin 5 mg/day, amlodipine 10 mg/day, and pravastatin 20 mg every night. He comes to the clinic with no complaints except for palpitations and shortness of breath when doing yard work. His vital signs include BP 138/80 mm Hg and HR 100 beats/minute. His international normalized ratio (INR) is 2.4, and his digoxin concentration is 1.1 ng/mL. All other laboratory results are within normal limits. Which is the best option to help with Z.G.'s symptoms?
   A. Add metoprolol succinate 50 mg/day.
   B. Increase digoxin to 0.25 mg/day.
   C. Add verapamil 240 mg/day.
   D. Continue current regimen and advise the patient to avoid activities that cause signs or symptoms.

6. R.P. is an 69-year-old Hispanic man with a history of HTN and gout. His medications include allopurinol 300 mg/day, amlodipine 10 mg/day, and aspirin 81 mg/day. His vital signs include BP 145/85 mm Hg and HR 82 beats/minute. His laboratory values are normal and his 10-year atherosclerotic cardiovascular disease (ASCVD) risk is 22.4%. Which is the best therapy for R.P.?
   A. Add hydrochlorothiazide 25 mg/day to achieve a systolic blood pressure (SBP) goal of less than 130 mm Hg.
   B. Add lisinopril 40 mg/day and titrate to achieve an SBP goal of less than 140.
   C. Add losartan 25 mg/day to achieve an SBP less than 130 mm Hg.
   D. Make no changes to his current medications because his SBP is at goal.

7. J.T. is a 58-year-old man who presents to his primary care provider for the first time in 10 years. He has smoked 2 packs/day for the past 30 years and takes no medication. A fasting lipid panel shows total cholesterol (TC) 222 mg/dL, low-density lipoprotein cholesterol (LDL-C) 105 mg/dL, triglycerides (TG) 330 mg/dL, and high-density lipoprotein cholesterol (HDL-C) 51 mg/dL. His vital signs include BP 140/75 mm Hg and HR 80 beats/minute. His pooled cohort equation reveals a 10-year ASCVD risk of 14.6%. Which would be the best pharmacologic therapy to initiate in J.T.?
   A. Initiate simvastatin 20 mg/day and gemfibrozil 600 mg twice daily.
   B. Initiate rosuvastatin 2.5 mg/day.
   C. Initiate pravastatin 20 mg/day and fenofibrate 160 mg/day.
   D. Initiate atorvastatin 20 mg/day.

8. J.S. is a 43-year-old man with HTN who presents for an annual physical examination. His family history is significant for his father having HTN. His only medication is lisinopril 10 mg/day. His BP is 145/90 mm Hg. A fasting lipid profile shows TC 238 mg/dL, TG 95 mg/dL, LDL-C 176 mg/dL, and HDL-C 43 mg/dL. His calculated 10-year ASCVD risk according to the pooled cohort equation is 3.9%. Which best describes the next step for management in J.S.?
   A. Initiate high-intensity statin therapy.
   B. Initiate fenofibrate 130 mg/day.
   C. Initiate moderate-intensity statin therapy.
   D. Do not initiate statin therapy and reevaluate risk in 4–6 years.

9. J.C. is a 62-year-old man (height 177.8 cm, weight 135 kg [1 month ago 143 kg]) with a history of diabetes, chronic kidney disease (CKD), bipolar disorder, CCD, and hypertriglyceridemia that, in the past, has resulted in pancreatitis. His family history is significant for his father having CCD and hypertriglyceridemia. He is not a smoker, but admits drinking a 6-pack of beer daily. Pertinent laboratory findings include a hemoglobin A1C of 11.6% and a serum creatinine (SCr) of 2.6 mg/dL. He currently takes atorvastatin 40 mg every evening, aspirin 81 mg/day, metformin 1000 mg twice daily, olanzapine 10 mg/day, metoprolol tartrate 50 mg twice daily, and coenzyme Q10 200 mg/day. His fasting lipid profile is TC 402 mg/dL, LDL-C unable to calculate, HDL-C 48 mg/dL, and TG 1500 mg/dL. His other laboratory values are within normal limits. Which best describes potential secondary causes of elevated TG concentrations that should be considered in J.C.?
   A. Obesity, poorly controlled diabetes, olanzapine, metoprolol, coenzyme Q10.
   B. Alcohol consumption, poorly controlled diabetes, weight loss, metoprolol.
   C. Obesity, metformin, hyperthyroidism, alcohol consumption.
   D. Alcohol consumption, obesity, poorly controlled diabetes, olanzapine, metoprolol.

Questions 10 and 11 pertain to the following case.

A.M. is a 32-year-old woman with type 1 diabetes and HTN. Her current medication regimen is as follows: ramipril 10 mg/day, chlorthalidone 25 mg/day, amlodipine 10 mg/day, ethinyl estradiol 20 mcg/norethindrone 1 mg daily (for the past 2 years), and insulin as directed. Her vital signs today include BP 145/83 mm Hg, repeated BP 145/81 mm Hg; HR 82 beats/minute; height 167.64 cm; weight 70 kg. A.M. presents to the clinic for HTN management. She has no new concerns but expresses that she would prefer not to take any more drugs, if possible.

10. Which option is the best clinical plan for A.M.?
    A. No change in therapy is currently warranted.
    B. Advise weight loss and recheck her BP in 3 months.
    C. Change chlorthalidone to hydrochlorothiazide.
    D. Discuss changing her contraceptive method.

11. A.M. and her husband have decided they are ready to have children. What is the best medication option for A.M.?
    A. No change in therapy is warranted.
    B. Discontinue ramipril and replace with labetalol.
    C. Increase chlorthalidone to 50 mg/day.
    D. Discontinue all antihypertensive therapy.

12. A 66-year-old African American man (height 177.8 cm, weight 91 kg) with AF and CCD (non–ST-segment elevation MI and stent placement 3 years ago) presents with palpitations. Rate control therapy, including trials of β-blockers and non-dihydropyridine calcium channel blockers, has been unsuccessful in controlling his symptoms. He currently takes metoprolol succinate 50 mg/day, aspirin 81 mg/day, atorvastatin 80 mg/day, lisinopril 5 mg/day, and warfarin 4 mg/day. His laboratory results show INR 2.2, potassium (K) 4.8 mEq/L, SCr 1.2 mg/dL. His BP is 110/70 mm Hg, and his HR is 95 beats/minute. Which is the best antiarrhythmic therapy for him?
    A. Disopyramide.
    B. Flecainide.
    C. Propafenone.
    D. Sotalol.

BPS Pharmacotherapy Specialty Examination Content Outline

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline, tested during the Spring 2024 window:

1. Patient-Centered Pharmacotherapy
   a. 1.1. Develop patient-centered, evidence-based pharmacotherapy plans. Subtasks: 1.1.1–1.1.3, 1.1.6–1.1.11, 1.1.14–1.1.17.
   b. 1.2. Monitor the patient to ensure safe and effective pharmacotherapy. Subtasks: 1.2.1, 1.2.2.
   c. 1.3. Modify pharmacotherapy plans through ongoing patient assessment. Subtasks: 1.3.1–1.3.7.
2. Application of Evidence to Practice and Education
   a. 2.2. Evaluate pharmacotherapy-related literature and health information. Subtasks: 2.2.1, 2.2.3, 2.2.6.

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline, tested during the Fall 2024 window:

1. Patient Care Specialty Areas
   a. 1A. Primary Pharmacotherapy Specialty Areas. Subtasks: 1A2, 1A4.
2. Therapeutics and Patient Management
   a. 2A. Treatment Planning. Subtasks: 2A1–2A6.
   b. 2B. Therapeutic Implementation. Subtasks: 2B1, 2B2.
   c. 2C. Treatment Outcomes and Monitoring. Subtasks: 2C1–2C4.
3. Professional Practice
   a. 3A. Quality of Care. Subtasks: 3A2, 3A4.
   b. 3B. Evidence-Based Practice. Subtasks: 3B1, 3B2.
   c. 3C. Practice Management. Subtask: 3C1.

I. HEART FAILURE

Patient Cases

1. L.S. is a 48-year-old woman with alcohol-induced cardiomyopathy. Her most recent LVEF is 20%; her daily activities are limited by dyspnea and fatigue (NYHA class III). Her medications include lisinopril 40 mg daily, furosemide 40 mg twice daily, carvedilol 12.5 mg twice daily, spironolactone 25 mg/day, and digoxin 0.125 mg/day. She has been stable on these doses for the past month. Her most recent laboratory results include sodium (Na) 140 mEq/L, potassium (K) 4.0 mEq/L, chloride 105 mEq/L, bicarbonate 26 mEq/L, blood urea nitrogen 12 mg/dL, SCr 0.8 mg/dL, glucose 98 mg/dL, calcium 9.0 mg/dL, phosphorus 2.8 mg/dL, magnesium 2.0 mEq/L, and digoxin 0.7 ng/mL. She weighs 69 kg, and her vital signs include BP 112/70 mm Hg and HR 72 beats/minute. In the clinic today, she has concerns for increased shortness of breath and fatigue. On physical examination, you note 2+ bilateral lower extremity pitting edema and hear crackles on inspiration. What is the best approach for maximizing the management of her HF?
   A. Increase carvedilol to 25 mg twice daily.
   B. Increase lisinopril to 80 mg/day.
   C. Add empagliflozin 10 mg/day.
   D. Increase digoxin to 0.25 mg/day.

2. J.T. is a 62-year-old man (height 182.88 cm, weight 85 kg) with a history of CCD (MI 3 years ago), HTN, depression, CKD (baseline SCr 2.8 mg/dL), PAD, osteoarthritis, hypothyroidism, and HF (LVEF of 25%). His medications include aspirin 81 mg/day, atorvastatin 40 mg every night, enalapril 5 mg twice daily, metoprolol succinate 50 mg/day, furosemide 80 mg twice daily, cilostazol 100 mg twice daily, acetaminophen 650 mg four times daily, sertraline 100 mg/day, and levothyroxine 0.1 mg/day. His vital signs include BP 128/74 mm Hg and HR 72 beats/minute. Pertinent laboratory results include K 4.1 mEq/L, SCr 2.8 mg/dL, and a thyroid-stimulating hormone of 2.6 mIU/L. His HF is stable and considered NYHA class II. What is the best approach for maximizing the management of his HF?
   A. Discontinue metoprolol and begin carvedilol 12.5 mg twice daily.
   B. Change enalapril to sacubitril/valsartan 24/26 mg orally twice daily.
   C. Add spironolactone 25 mg/day.
   D. Add digoxin 0.125 mg/day.

A. Background: HF is a complex clinical syndrome caused by any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood.
   1. Prevalence
      a. Affects 6.2 million Americans
      b. Prevalence increases with age
   2. Heart failure with reduced ejection fraction (HFrEF)
      a. Defined as a clinical diagnosis of HF and an LVEF of 40% or less
      b. Dilated ventricle
      c. Two thirds of cases are attributable to chronic coronary disease (CCD).
      d. One third of cases are attributable to nonischemic cardiomyopathy.
         i. HTN
         ii. Thyroid disease
         iii. Obesity
         iv. Stress (Takotsubo)

v. Cardiotoxins
   (a) Alcohol
   (b) Cocaine
   (c) Chemotherapeutic agents
      (1) Anthracyclines
      (2) Cyclophosphamide (high dose)
      (3) Fluorouracil
      (4) Trastuzumab with or without pertuzumab/hyaluronidase
      (5) Mitoxantrone
vi. Myocarditis
vii. Idiopathic
viii. Tachycardia
ix. Peripartum

3. Heart failure with preserved EF (HFpEF)
   a. Defined as an LVEF of 50% or greater
   b. Accounts for about 50% (highly variable) of patients with HF
   c. Impaired ventricular relaxation and filling
   d. Normal wall motion
   e. Most common cause is HTN (60%–89%).
4. Primary symptoms
   a. Dyspnea
   b. Fatigue
   c. Edema
   d. Exercise intolerance
5. Stages and functional class of HF according to the American College of Cardiology/American Heart Association (ACC/AHA) (Table 1)

Table 1. HF Stages and Corresponding NYHA Functional Class

ACC/AHA Stage		NYHA Functional Class	
A	**At risk of HF:** At high risk of HF (uncontrolled risk factors) but without structural heart disease, cardiac biomarkers of stretch or injury, or symptoms of HF	None	
B	**Pre-HF:** No signs or symptoms of HF but with structural heart disease, increased filling pressures, and/or risk factors + either increased BNP or persistently elevated troponin	I	Asymptomatic HF; no limitations in physical activity caused by HF symptoms
C	**Symptomatic HF:** Structural heart disease with prior or current symptoms of HF	I	No limitations in physical activity caused by HF symptoms
		II	Slight limitation of physical activity; asymptomatic at rest, but symptoms of HF with normal level of activity
		III	Marked limitations in physical activity because of HF symptoms; asymptomatic at rest
		IV	Symptoms of HF at rest or unable to carry out any physical activity

Table 1. HF Stages and Corresponding NYHA Functional Class (*Cont'd*)

ACC/AHA Stage		NYHA Functional Class	
D	**Advanced HF:** Marked HF symptoms that interfere with daily life and recurrent hospitalizations despite attempts to optimize guideline-directed medical therapy	IV	Symptoms of HF at rest

ACC = American College of Cardiology; AHA = American Heart Association; HF = heart failure; NYHA = New York Heart Association.

Adapted from: 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2022;79:1757-80.

6. Goals of therapy
    a. Modify or control risk factors (e.g., HTN, obesity, diabetes)
    b. Manage structural heart disease
    c. Reduce morbidity and mortality
    d. Prevent or minimize sodium and water retention
    e. Eliminate or minimize HF symptoms
    f. Block compensatory neurohormonal activation caused by reduced cardiac output (CO)
    g. Slow progression of worsening cardiac function

B. HFrEF
    1. Pharmacologic therapy (Figure 1)
        a. General approach to therapy
            i. Initiation and titration of optimal medication therapy in HFrEF should prioritize angiotensin receptor-neprilysin inhibitor (ARNI), β-blocker, mineralocorticoid receptor antagonist (MRA), and sodium-glucose cotransporter 2 (SGLT2) inhibitor use to reduce CV mortality and HF hospitalizations.
            ii. The order of medication initiation does not necessarily need to follow the sequence of trial publications. Rather, an individualized approach to initiation and sequencing guided by patient symptoms, vital signs, tolerance, renal function, electrolytes, comorbidities, functional status, and ability to follow up is recommended.
            iii. Titration and optimization can occur as frequently as every 1–2 weeks.
            iv. After optimizing ARNI, β-blocker, MRA, SGLT2 inhibitor, and diuretic therapy, additional agents can be considered on the basis of patient factors.
        b. ACE inhibitors
            i. Place in therapy:
                (a) Recommended in all patients with HFrEF and current or prior symptoms when use with an ARNI is not feasible, unless contraindicated (class I indication)
                (b) Often better tolerated than ß-blockers as first-line agents in patients with signs and symptoms of congestion/fluid overload
            ii. Benefits
                (a) Decreased mortality (about 25%–50% relative risk reduction compared with placebo depending on severity of HF)
                (b) Decreased hospitalizations (about 30% relative risk reduction compared with placebo)
                (c) Symptom improvement
                (d) Improved clinical status
                (e) Improved sense of well-being
                (f) Notable trials: CONSENSUS (enalapril), SOLVD (enalapril), SAVE (captopril), AIRE (ramipril), and TRACE (trandolapril).

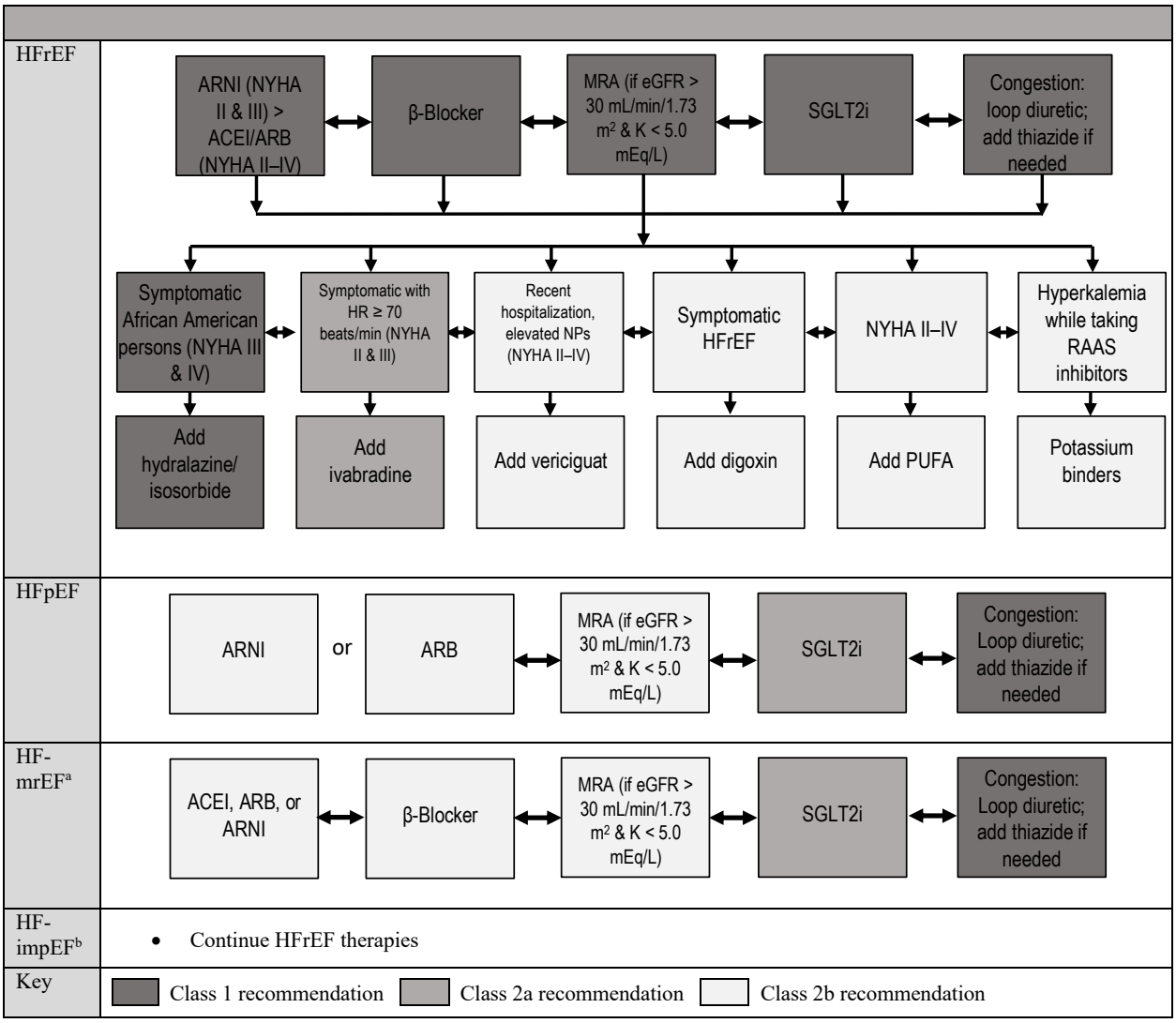


Figure 1. Updated heart failure treatment algorithms.

[a]HFmrEF is defined as a left ventricular ejection fraction (LVEF) of 41%–49% with evidence of spontaneous or provokable increased LV filling pressure.

[b]HFimpEF is defined as HF with a previous LVEF ≤ 40% and a follow-up measurement of LVEF > 40%.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; eGFR = estimated glomerular filtration rate; HF = heart failure; HFimpEF = heart failure with improved ejection fraction; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; MRA = mineralocorticoid receptor blocker (e.g., spironolactone, eplerenone); NP = natriuretic peptide; NYHA = New York Heart Association; PUFA = polyunsaturated fatty acid; RAAS = renin-angiotensin-aldosterone system; SGLT2i = sodium-glucose cotransporter 2 inhibitor.

iii. Mechanism of action
  (a) Blocks production of angiotensin II
    (1) Decreases sympathetic stimulation
    (2) Decreases production of aldosterone and vasopressin
    (3) Decreases vasoconstriction (afterload and preload)
  (b) Increases bradykinins (decreases their metabolism)
    (1) Increases vasodilatory prostaglandins

(2) May attenuate myocardial remodeling

iv. Dosing and administration considerations
   (a) Start low and double the dose every 1–4 weeks to target dose (Table 2).
   (b) ATLAS trial comparing patients with systolic dysfunction who received low-dose lisinopril (2.5–5 mg/day) and patients who received high-dose lisinopril (32.5–35 mg/day) showed no difference in all-cause mortality or CV mortality; however, the high-dose group did have a significant 12% lower risk of death or hospitalization for any reason and 24% fewer hospitalizations for HF.
   (c) Patients may notice improvement in symptoms in several weeks.
   (d) Avoid use in patients who have experienced angioedema as the result of previous ACE inhibitor use or those who are pregnant or plan to become pregnant.
   (e) Use caution if SBP is less than 80 mm Hg, SCr is greater than 3 mg/dL, K is greater than 5.0 mEq/L, or the patient has bilateral renal artery stenosis.

v. Monitoring
   (a) Monitor SCr and K for 1–2 weeks after initiating therapy or increasing the dose, especially in high-risk patients (preexisting hypotension, diabetes, K supplements, azotemia). SCr may rise (up to a 30% increase is acceptable) because of renal efferent artery dilation (results in a slightly decreased glomerular filtration rate [GFR]). Rarely, acute renal failure occurs, especially if the patient is intravascularly depleted. Be careful to avoid overdiuresis.
   (b) Monitor BP and symptoms of hypotension (e.g., dizziness, lightheadedness).
      (1) BP may be low to begin with because of low CO.
      (2) BP = CO × Systemic vascular resistance (SVR).
      (3) In HF, as CO increases because of decreased SVR, BP may decrease slightly or remain the same.
      (4) Symptoms of hypotension are often not present with small dose increases. Remember to treat the patient, not the number.
   (c) Ninety percent of people tolerate ACE inhibitors.
      (1) Angioedema (less than 1%): Can switch to angiotensin II receptor blockers (ARBs; cross-reactivity is 2.5%) or hydralazine–isosorbide dinitrate
      (2) Cough (20%): Can switch to ARBs (less than 1%)

Table 2. ACE Inhibitors and Recommended Dosing

Drug	Starting Dosage	Target Dosage
Captopril	6.25 mg three times daily	50 mg three times daily
Enalapril	2.5 mg twice daily	10 mg twice daily
Lisinopril	2.5–5 mg daily	20 mg daily
Perindopril	2 mg daily	8 mg daily
Ramipril	1.25–2.5 mg daily	10 mg daily
Trandolapril	1 mg daily	4 mg daily

Note: Fosinopril and quinapril can be used; however, they do not have the same magnitude of mortality-reducing data as listed above.
ACE = angiotensin-converting enzyme

c. Angiotensin II receptor blockers (ARBs)
   i. Place in therapy
      (a) Recommended in patients with HFrEF with current or prior symptoms who are unable to take an ACE inhibitor or ARNI (class I indication). Have not been proven superior to ACE

inhibitors at target HF dosages.
(b) Possibly considered if patient has experienced ACE inhibitor–induced angioedema (cross-reactivity 2.5%)
(c) Often better tolerated than ß-blockers as first-line agents in patients with signs and symptoms of congestion/fluid overload

ii. Benefits
(a) Decreased HF-related hospitalizations and decreased death from CV causes.
(b) Notable clinical trials: CHARM-Alternative (candesartan), VALIANT (valsartan), VAL-HEFT (valsartan), and HEAAL (losartan).

iii. Mechanism of action
(a) Selectively block the binding of angiotensin II to the angiotensin I receptor
(b) Deters vasoconstriction and aldosterone-secreting effects
(c) Does not affect ACE or inhibit kinin catabolism

iv. Dosing and administration
(a) Start low and double the dose every 1–4 weeks to target dose (Table 3).
(b) Patients may notice improvement in symptoms in several weeks.
(d) Avoid use in patients who have angioedema because of previous ARB use or those who are pregnant or plan to become pregnant.
(e) Use caution if SBP is less than 80 mm Hg, SCr is greater than 3 mg/dL, K is greater than 5.0 mEq/L, or the patient has bilateral renal artery stenosis.

v. Monitoring
(a) SCr and K 1–2 weeks after initiating therapy or increasing the dose, especially in high-risk patients (preexisting hypotension, diabetes, K supplements, azotemia)
(1) SCr may rise (up to a 30% increase is acceptable) because of renal efferent artery dilation (results in a slightly decreased GFR).
(2) Rarely, acute renal failure occurs, especially if the patient is intravascularly depleted (be careful to avoid overdiuresis).
(b) Monitor BP and symptoms of hypotension (e.g., dizziness, lightheadedness).
(c) Other adverse reactions
(1) Angioedema (rare)
(2) Cough (less than 1%)

Table 3. ARBs and Recommended Dosing

Drug	Starting Dosage	Target Dosage
Candesartan	4–8 mg daily	32 mg daily
Losartan	25–50 mg daily	150 mg daily
Valsartan	20–40 mg twice daily	160 mg twice daily

ARB = angiotensin receptor blocker.

d. Sacubitril/valsartan
i. Place in therapy
(a) According to the 2022 ACC/AHA/Heart Failure Society of America (HFSA) HF guidelines
(1) ARNIs are recommended for patients with chronic HFrEF to reduce morbidity and mortality (class I recommendation). ARNIs are recommended over ACE inhibitors or ARBs, when feasible (class I recommendation), as part of a direct-to-ARNI approach.
(2) In patients with chronic symptomatic NYHA class II or III HFrEF who can tolerate an ACE inhibitor or ARB, replacement by sacubitril/valsartan is recommended to

further reduce morbidity and mortality (class I recommendation).

ii. Benefits
  (a) Decreased composite endpoint of death from CV causes or hospitalization for HF (20% relative risk reduction compared with enalapril monotherapy)
  (b) Decreased all-cause mortality (16% relative risk reduction) and CV death (20% relative risk reduction) compared with enalapril monotherapy
  (c) Decreased hospitalization for HF (21% relative risk reduction compared with enalapril monotherapy)
  (d) Notable clinical trial: PARADIGM-HF

iii. Mechanism of action
  (a) Sacubitril—prodrug metabolized to an active metabolite that inhibits neprilysin, increasing levels of natriuretic peptides
  (b) Valsartan—ARB, selectively blocks the angiotensin I receptor and inhibits angiotensin II–dependent aldosterone release

iv. Dosing and administration considerations
  (a) Initial dose
    (1) Not currently taking ACE inhibitor or ARB, switching from low dose ACE inhibitor (e.g., total daily dose of enalapril ≤10 mg, lisinopril ≤ 10 mg, ramipril ≤5 mg, or equivalent) or ARB (e.g., total daily dose of valsartan ≤160 mg, losartan ≤50 mg, olmesartan ≤10 mg, or equivalent), or estimated GFR (eGFR) <30 mL/min/m^2: sacubitril 24 mg/valsartan 26 mg twice daily
    (2) Switching from a standard dose ACE inhibitor (e.g., total daily dose of enalapril >10 mg, lisinopril >10 mg, ramipril >5 mg, or equivalent) or ARB (e.g., total daily dose of valsartan >160 mg, losartan >50 mg, olmesartan >10 mg, or equivalent): sacubitril 49 mg/valsartan 51 mg twice daily
  (b) Maintenance dose: Double the dose every 2–4 weeks to a target dose of sacubitril 97 mg/valsartan 103 mg twice daily, as tolerated.
  (c) If switching from an ACE inhibitor, allow a 36-hour washout period before initiating sacubitril/valsartan.
  (d) Because sacubitril is a neprilysin inhibitor, BNP will increase with use. However, NT-proBNP levels will not change.

v. Monitoring
  (a) Observe for signs and symptoms of angioedema (contraindicated in patients with a history of angioedema).
  (b) Observe for signs and symptoms of hypotension; hypotension occurs more commonly than with ARB use alone..
  (c) Monitor renal function and K 1–2 weeks after initiating therapy or increasing the dose, especially in high-risk patients (e.g., preexisting hypotension, diabetes, K supplements, azotemia).
  (d) Monitor fluid status because patients may require a dose reduction in diuretic therapy.

e. β-blockers
  i. Place in therapy:
    (a) Recommended in all patients with HFrEF with current or prior symptoms unless contraindicated (class I indication)
    (b) Often better tolerated than than ACE inhibitors/ARBs/angiotensin receptor-neprilysin inhibitors (ARNIs) as first-line agents in patients without signs and symptoms of congestion/fluid overload
  ii. Benefits (when added to an ACE inhibitor)
    (a) Decreased mortality (about 35% relative risk reduction compared with placebo)

(b) Decreased hospitalizations (about 25% relative risk reduction compared with placebo)
(c) Symptom improvement
(d) Improved clinical status
(e) Notable clinical trials: CIBIS II (bisoprolol), MERIT-HF (metoprolol succinate), COPERNICUS (carvedilol), and COMET (metoprolol tartrate vs. carvedilol).

iii. Mechanism of action
(a) Blocks the effect of norepinephrine and other sympathetic neurotransmitters on the heart and vascular system
(1) Decreases ventricular arrhythmias (sudden cardiac death)
(2) Decreases cardiac hypertrophy and cardiac cell death
(3) Decreases vasoconstriction and HR
(b) Carvedilol also provides α_1-blockade.
(1) Further decreases SVR (afterload)
(2) Results in greater reduction in BP than metoprolol succinate

iv. Dosing and administration considerations
(a) Only bisoprolol, carvedilol, and metoprolol succinate are recommended in HFrEF.
(b) Initiate when HF symptoms are stable and patients are euvolemic.
(c) Should not be prescribed without diuretics in patients with current or recent history of fluid retention.
(d) Start low and increase (double) the dose every 1– 2 weeks (or slower, if needed) to target dose. Aim to achieve target dose in 8–12 weeks (Table 4).
(e) Avoid abrupt discontinuation; can precipitate clinical deterioration
(f) Might not notice improvement in symptoms for several months
(g) Should be considered even in patients with reactive airway disease or asymptomatic bradycardia

Table 4. β-Blockers and Recommended Dosing

Agent	Starting Dosage	Target Dosage
Bisoprolol	1.25 mg daily	10 mg daily
Carvedilol	3.125 mg twice daily	25 mg twice daily[a]
Carvedilol CR	10 mg daily	80 mg daily
Metoprolol succinate	12.5–25 mg daily	200 mg daily

[a]50 mg twice daily if weight > 85 kg.
CR = controlled release

v. Monitoring
(a) BP, HR, and symptoms of hypotension or bradycardia (monitor in 1–2 weeks)
(1) Significant hypotension, bradycardia, or dizziness occurs in about 1% of patients when the β-blocker is titrated slowly. If these symptoms appear, lower the dose by 50%.
(2) Of importance, remember that higher β-blocker doses are associated with greater mortality reduction. Therefore, if hypotension alone is the problem, try reducing the ACE inhibitor (or another antihypertensive) first or scheduling one agent at bedtime and one in the morning.
(b) Increased edema or fluid retention (monitor in 1–2 weeks)
(1) One percent to 2% more common than with placebo (in euvolemic, stable patients)
(2) Responds to diuretic increase
(3) Do not increase ß-blocker dose during episodes of fluid retention after therapy

initiation or dose titration.

(c) Fatigue or weakness
(1) One percent to 2% more common than with placebo
(2) Usually resolves spontaneously in several weeks
(3) May require dosage decrease or discontinuation

f. Mineralocorticoid receptor antagonists (MRAs)
i. Place in therapy
(a) Recommended in patients with NYHA class II–IV to reduce morbidity and mortality unless a contraindication exists (class I indication).
ii. Benefits of spironolactone in NYHA class III and IV HF (RALES trial)
(a) Decreased mortality (30% relative risk reduction compared with placebo)
(b) Decreased hospitalizations for HF (35% relative risk reduction compared with placebo)
(c) Improved symptoms
iii. Benefits of eplerenone (selective MRA) in NYHA class II HF (EMPHASIS-HF)
(a) Decreased composite endpoint of death from CV causes or hospitalization from HF (37% relative risk reduction compared with placebo)
(b) Decreased death from CV causes (24% relative risk reduction compared with placebo)
(c) Decreased hospitalizations for HF (42% relative risk reduction compared with placebo)
(d) Decreased mortality (24% relative risk reduction compared with placebo)
iv. Benefits of eplerenone in left ventricular dysfunction after MI (EPHESUS)
(a) Decreased mortality (15% relative risk reduction compared with placebo)
(b) Decreased composite endpoint of death from CV causes or hospitalization for CV events (13% relative reduction compared with placebo)
v. Mechanism of action
(a) Blocks effects of aldosterone in the kidneys, heart, and vasculature
(b) Decreases K and magnesium loss; decreases ventricular arrhythmias
(c) Decreases Na retention; decreases fluid retention
(d) Eliminates catecholamine potentiation; decreases BP
(e) Blocks direct fibrotic actions on the myocardium
vi. Dosing and administration considerations
(a) eGFR should be greater than 30 mL/minute/1.73 m^2), and K should be less than 5.0 mEq/L (Table 5).

Table 5. MRAs and Recommended Dosing

	eGFR ≥ 50 mL/min/1.73 m^2		**eGFR 30-49 mL/min/1.73 m^2**	
	Initial dose	**Maintenance dose**	**Initial dose**	**Maintenance dose**
Eplerenone	25 mg daily	50 mg daily	25 mg every other day	25 mg daily
Spironolactone	12.5–25 mg daily	25 mg daily or BID	12.5 mg daily or every other day	12.5–25 mg daily

BID = twice daily; eGFR = estimated glomerular filtration rate; MRA = mineralocorticoid receptor antagonist.

vii. Monitoring
(a) K and SCr should routinely be monitored according to patient status, at about 1 week, 1 month, and 6 months after initiating or increasing MRA therapy. More frequent monitoring is appropriate in the setting of clinical instability. If the dose of ACE inhibitor or ARB is increased, restart monitoring.
(1) Hyperkalemia was reported in 2% or less of the patients in trials; however, in practice, it occurs in about 20% of patients.

(2) Decrease dose by 50% or discontinue if K is greater than 5.5 mEq/L.
(b) Gynecomastia
(1) Spironolactone: Reported at a rate of 10% in clinical trials
(2) Eplerenone can be considered as an alternative to spironolactone if gynecomastia is present.

g. SGLT2 inhibitors
i. Place in therapy
(a) Recommended in symptomatic HFrEF with adequate renal function regardless of diabetes status
(1) Dapagliflozin: Indicated if eGFR is 25 mL/minute/1.73 m^2 or greater
(2) Empagliflozin: Indicated if eGFR is 20 mL/minute/1.73 m^2 or greater
ii. Benefits
(a) Dapagliflozin (DAPA-HF) and empagliflozin (EMPEROR-Reduced) have been shown to reduce the risk of CV death or worsening HF.
iii. Mechanism of action
(a) Inhibit the SGLT2 cotransporter in the renal proximal tubules, reducing reabsorption of filtered glucose and increasing urinary glucose excretion
(b) Promote diuresis, reduce arterial pressure, and may reduce cardiac hypertrophy and fibrosis
iv. Dosing
(a) Dapagliflozin: 10 mg orally daily
(b) Empagliflozin: 10 mg orally daily
v. Monitoring
(a) Monitor SCr, signs and symptoms of volume depletion, and orthostatics. Consider reducing diuretic dose because of diuretic effects.
(b) Monitor blood glucose.
(c) Assess patients presenting with signs or symptoms of metabolic acidosis for ketoacidosis. Patients may experience euglycemic diabetic ketoacidosis. Discontinue SGLT2 inhibitors 3–5 days before surgery to reduce the risk.
(d) Monitor for signs and symptoms of mycotic genital infections and urinary tract infections.

h. Hydralazine/isosorbide dinitrate
i. Place in therapy
(a) Recommended in addition to optimal medical therapy to reduce morbidity and mortality for patients self-described as African American with NYHA class III or IV HFrEF (class I indication)
(b) May be useful in patients with current or prior symptoms of HFrEF who are unable to tolerate an ARNI, ACE inhibitor, or an ARB (class IIa indication)
ii. Benefits
(a) Decreased mortality (43% relative risk reduction compared with placebo in African American patients)
(b) Reduced pulmonary congestion and improved exercise tolerance
(c) Notable clinical trials: V-HeFT and A-HeFT
iii. Mechanism of action
(a) Hydralazine
(1) Arterial vasodilator (reduces afterload)
(2) Increases effect of nitrates through antioxidant mechanisms
(b) Isosorbide dinitrate
(1) Stimulates nitric acid signaling in the endothelium

(2) Venous vasodilator (reduces preload)

iv. Dosing and administration considerations
  (a) Fixed-dose BiDil (hydralazine 37.5 mg plus isosorbide dinitrate 20 mg) starting at 1 tablet three times daily with a goal dose of 2 tablets three times daily
  (b) Hydralazine 75 to 300 mg daily in 3 or 4 divided doses; isosorbide dinitrate 60–120 mg daily in 3 or 4 divided doses

v. Monitoring
  (a) Headache
  (b) Hypotension
  (c) Drug-induced lupus (dose-dependent with hydralazine)

i. Diuretics
  i. Place in therapy: Indicated in patients with evidence of fluid retention (class I indication)
  ii. Short-term benefit (days)
    (a) Decreased jugular venous distension
    (b) Decreased pulmonary congestion
    (c) Decreased peripheral edema
  iii. Intermediate-term benefits (weeks to months)
    (a) Decreased daily symptoms
    (b) Increased exercise tolerance
  iv. Long-term benefits (months to years): No benefit on mortality
  v. Mechanism of action: Inhibit reabsorption of Na in the ascending limb of the loop of Henle (loops) or in the distal tubule (thiazides)
  vi. Dosing and administration considerations (Table 6)
    (a) Should be combined with guideline-directed medical therapy
    (b) Start with a low initial dose and then double the dose and titrate according to the patient's weight as needed. Bioavailability differs between oral loop diuretics and must be considered when converting from one agent to another.
    (c) If a patient has fluid overload, initiate and adjust therapy to result in 0.5-1 kg of weight loss per day (may be more aggressive in the inpatient setting).
    (d) Long-term therapy should be adjusted to maintain a euvolemic state.
    (e) A loop diuretic can be combined with another diuretic class (e.g., thiazide diuretic) for synergy, if needed.
    (f) Loop diuretics are preferred because of their greater diuretic capabilities; loop diuretics also retain efficacy with decreased renal function.
  vii. Monitoring: Monitor and replace K and magnesium as needed, especially with loop diuretics (goal with CVD is K of 4.0 mEq/L or greater and magnesium of 2.0 mEq/L or greater to minimize the risk of arrhythmias). Monitor SCr and blood urea nitrogen (BUN) to avoid acute kidney injury with overdiureses. Also monitor HCO_3 for metabolic alkalosis with overdiuresis.

Table 6. Diuretics and Recommended Dosing[a]

Agent	Oral Bioavailability (%)	Initial Daily Dose	Maximal Total Daily Dose (mg)	Duration of Action (hr)
Loop Diuretics (inhibit 20%–25% of sodium reabsorption)				
Furosemide[b]	10–67	20–40 mg daily or BID	600	6–8
Bumetanide[b]	80–100	0.5–1 mg daily or BID	10	4–6
Torsemide	80–100	10–20 mg daily	200	12–16
Ethacrynic acid[b]	100	25–50 mg daily or BID	200	6–8

Table 6. Diuretics and Recommended Dosing[a] *(Cont'd)*

Agent	Oral Bioavailability (%)	Initial Daily Dose	Maximal Total Daily Dose (mg)	Duration of Action (hr)
Hydrochlorothiazide	65–75	25 mg daily or BID	200	6–12
Metolazone	40–65	2.5 mg daily	20	12–24
Chlorthalidone	64	12.5–25 mg daily	100	24–72
Chlorothiazide[b]	30–50	250–500 daily or BID	1000	6–12

[a]Equivalent doses: furosemide 40 mg = bumetanide 1 mg = torsemide 10–20 mg = ethacrynic acid 50 mg.
[b]Available in oral and intravenous formulations.
BID = twice daily.

j. Ivabradine
   i. Place in therapy
      (a) Novel therapy approved by the FDA in 2015
      (b) According to the 2022 ACC/AHA/Heart Failure Society of America HF guidelines, ivabradine can be beneficial to reduce HF hospitalizations for patients with symptomatic (NYHA class II and III), stable, chronic HFrEF (LVEF of 35% or less) who are receiving evidence-based therapies, including a β-blocker at maximum tolerated dose, and who are in sinus rhythm (SR) with an HR of 70 beats/minute or greater at rest (class IIa recommendation).
   ii. Benefits
      (a) Decreased composite endpoint of CV death or hospitalization for HF (18% relative risk reduction compared with placebo)
      (b) Decreased hospitalization for HF (26% relative risk reduction compared with placebo)
      (c) Notable clinical trial: SHIFT
   iii. Mechanism of action: Selectively inhibits the I_f current in the sinoatrial node, providing HR reduction
   iv. Dosing and administration considerations
      (a) Given the well-proven mortality benefits of β-blocker therapy, patients should be receiving β-blockers at maximally tolerated or target doses or have a contraindication to β-blocker therapy before assessing the resting HR for consideration of ivabradine initiation.
      (b) Initial dosing: Age younger than 75: 5 mg twice daily with food; age 75 and older: 2.5 mg twice daily with food
      (c) After 2–4 weeks, adjust dose according to HR:
         (1) Resting HR greater than 60 beats/minute: Increase dose by 2.5 mg twice daily until reaching the maximum dose of 7.5 mg twice daily.
         (2) Resting HR 50–60 beats/minute: Continue current dose.
         (3) Resting HR less than 50 beats/minute or signs/symptoms of bradycardia: Decrease dose by 2.5 mg twice daily or discontinue if already at 2.5 mg twice daily.
      (d) Maximum dose: 7.5 mg twice daily
      (e) Contraindications: Acute heart failure, BP <90/50 mm Hg, resting HR <60 beats/min before initiation, sinoatrial block, concomitant use with strong CYP3A4 inhibitors, severe hepatic impairment (Child-Pugh class C)
   v. Monitoring
      (a) Assess HR and rhythm for bradycardia (6%–10%) and AF (5%–8%) after 2 weeks of therapy initiation or modification and periodically thereafter

(b) Phosphenes (3%): transient rings or spots of light in the visual field

k. Digoxin
   i. Place in therapy: Can be beneficial in decreasing hospitalizations in patients with HFrEF (class IIb indication); should be added after guideline-directed medical therapy
   ii. Benefits
      (a) Improved symptoms
      (b) Improved exercise tolerance
      (c) Decreased hospitalizations (28% relative risk reduction compared with placebo)
      (d) No effect on mortality
      (e) Notable clinical trial: DIG
   iii. Mechanism of action (in HF)
      (a) Inhibits myocardial Na-K adenosine triphosphatase
      (b) Decreases central sympathetic outflow by sensitizing cardiac baroreceptors
      (c) Decreases renal reabsorption of Na
      (d) Minimal increase in cardiac contractility
   iv. Dosing and administration considerations
      (a) For most patients, 0.125 mg/day is adequate to achieve the desired serum concentration.
      (b) Consider dosing 0.125 mg every other day in patients older than 70 years, those with impaired renal function, or those with low lean body mass.
      (c) No indication to load patients with digoxin in the setting of HF
      (d) Avoid abrupt discontinuation; can precipitate clinical deterioration
      (e) Drug interactions: Digoxin concentrations are increased with concomitant:
         (1) Clarithromycin, erythromycin
         (2) Amiodarone (reduce digoxin dose by 30%–50% or reduce dosing frequency)
         (3) Dronedarone (reduce digoxin dose by 50%)
         (4) Itraconazole, posaconazole
         (5) Cyclosporine, tacrolimus
         (6) Verapamil
   v. Monitoring
      (a) Serum concentrations should be less than 1 ng/mL; in general, concentrations of 0.5–0.9 ng/mL are suggested. Serum concentrations should be obtained as a trough or at least 6–8 hours after the last dose.
         (1) Minimizes the risk of adverse effects and ventricular arrhythmias associated with increased concentrations.
         (2) Risk of toxicity increases with age and renal impairment.
         (3) Risk of toxicity increases in the presence of hypokalemia, hypomagnesemia, or hypercalcemia.
         (4) Signs of toxicity generally include nausea, vomiting, vision changes.
      (b) SCr should be monitored because the drug is primarily cleared renally.

l. Vericiguat
   i. Place in therapy: May be considered in addition to optimized HF therapy to reduce HF hospitalizations and CV death in patients at high risk with worsening HFrEF (VICTORIA trial) (class IIb recommendation)
   ii. Benefits: Reduced the composite of death from CV causes or first hospitalization for HF compared with placebo in patients with NYHA class II–IV HF with LVEF less than 45%
   iii. Mechanism of action: Soluble guanylate cyclase stimulator that enhances production of cyclic guanosine monophosphate and enhances sensitivity to endogenous nitric oxide, resulting in

smooth muscle relaxation and vasodilation

iv. Dosing and administration considerations:
  (a) Initiate at 2.5 mg orally once daily and titrate to a target of 10 mg orally once daily.
  (b) Take with food.
  (c) Contraindicated in pregnancy

v. Monitoring
  (a) Monitor blood pressure for hypotension. Dose may safely be increased when SBP is 100 mm Hg or greater up to 10 mg target dose. If SBP is 90–99 mm Hg, maintain current dose. If SBP is less than 90 mm Hg, decrease dose or discontinue therapy if patient is taking 2.5 mg and has symptomatic hypotension.
  (b) Monitor for syncope.
  (c) Drug interactions: Concomitant therapy with phosphodiesterase type 5 inhibitors, riociguat, and long-acting nitrates should be avoided because of enhanced hypotensive effects.

m. Polyunsaturated fatty acids (PUFAs)

i. Place in therapy: Reasonable adjunctive therapy to reduce mortality and CV hospitalizations (GISSI-HF and REDUCE-IT trials) (class 2b recommendation). Both icosapent ethyl, a highly purified eicosapentaenoic acid (EPA), and combined EPA/docosahexaenoic acid (DHA) are included in the guidelines.

ii. Benefits: In clinical trials, reduced the risk of death or hospital admission for CV event

iii. Mechanism of action: Reduce production of very-low-density lipoproteins. The exact mechanisms resulting in CV outcome benefits remain unknown.

iv. Dosing and administration considerations
  (a) Icosapent ethyl: 2 g orally twice daily
  (b) EPA/DHA formulations: 1000 mg of omega-3 PUFA orally daily (850 mg of EPA and 882 mg of DHA)
  (c) Take either formulation with food.

v. Monitoring
  (a) Bleeding events
  (b) A dose-related risk of AF has been reported.

n. Potassium binders

i. Place in therapy: May be considered to improve outcomes in patients who experience hyperkalemia (K 5.5 mEq/L or greater) while taking a renin-angiotensin-aldosterone inhibitor (PEARL-HF and HARMONIZE trials) (class 2b recommendation). Patiromer and sodium zirconium cyclosilicate are the agents included in the 2022 AHA/ACC/HFSA guidelines.

ii. Benefits
  (a) In clinical trials, potassium binders resulted in lower potassium concentrations and less hyperkalemia.
  (b) Patiromer has been shown to increase the number of patients able to increase spironolactone dose to 50 mg compared with placebo.
  (c) Clinical benefits have not yet been established.

iii. Mechanism of action
  (a) Patiromer exchanges calcium for potassium in the GI tract, increasing potassium excretion.
  (b) Sodium zirconium cyclosilicate exchanges sodium and hydrogen for potassium in the GI tract, increasing potassium excretion.

iv. Dosing and administration considerations
  (a) Patiromer
    (1) Powder for reconstitution that may be mixed with water, other beverages, or soft foods like applesauce or pudding

(2) Administer other oral medications at least 3 hours before or after patiromer.
(b) Sodium zirconium cyclosilicate
(1) Powder for reconstitution that should be mixed with at least 3 tablespoons of water before administration
(2) Administer other oral medications at least 2 hours before or after sodium zirconium cyclosilicate.
v. Monitoring
(a) Patiromer: Monitor for hypomagnesemia.
(b) Sodium zirconium cyclosilicate: Monitor for edema.
o. Other medication therapies
i. Anticoagulation
(a) Recommended for HF with permanent, persistent, or paroxysmal AF with an additional risk factor for stroke
(b) Reasonable for patients with HF who have permanent, persistent, or paroxysmal AF without an additional risk factor for stroke
(c) Not recommended in the absence of venous thromboembolism, AF, previous thromboembolic event, or a cardioembolic source
ii. Statins: Not recommended solely on the basis of HF diagnosis
iii. Antiarrhythmics: Given the neutral effects on mortality, the preferred antiarrhythmics in patients with HFrEF are dofetilide (AF/atrial flutter) and amiodarone.
iv. Nondihydropyridine (DHP) calcium channel blockers (CCBs) with negative inotropic effects can be harmful in patients with a low EF and should be avoided (class III recommendation: harm).
v. DHP CCBs: DHP CCBs have no proven benefit on morbidity or mortality in HF. Use of amlodipine can be considered for HTN or ischemic heart disease management in HF patients because of its neutral effects on morbidity and mortality.
p. Device therapy
i. Implantable cardioverter defibrillator recommended for primary prevention of sudden cardiac death in the following patients with ischemic or nonischemic HFrEF:
(a) Patients with ischemic or nonischemic HFrEF (LVEF of 35% of less) and NYHA class II or III symptoms on chronic optimal medical therapy. Life expectancy should be greater than 1 year, and patient must be at least 40 days post-MI (class I indication).
(b) Patients with HFrEF (LVEF of 30% or less) resulting from previous MI and NYHA class I symptoms on chronic optimal medical therapy. Life expectancy should be greater than 1 year, and patient should be at least 40 days post-MI (class I indication).
ii. Chronic resynchronization therapy recommended for those with an LVEF of 35% or less, in SR, and a left bundle branch block with a QRS of 150 milliseconds or greater on optimal medical therapy with NYHA class II–III symptoms or NYHA class IV with ambulation

2. Nonpharmacologic therapy
a. Prevent further cardiac injury.
i. Discontinue smoking.
ii. Reduce weight if obese.
iii. Control HTN (goal BP < 130/80 mm Hg per the 2022 ACC/AHA/Heart Failure Society of America HF guidelines)
iv. Control diabetes.
v. Decrease alcohol intake to 2 or fewer drinks per day for men and 1 or fewer drinks per day for women. Eliminate alcohol intake if cardiomyopathy is alcohol induced.
vi. Avoid excessive sodium intake (AHA recommends less than 2300 mg/day for general CV health promotion).
vii. Treat sleep apnea.

viii. Educate patient about appropriate self-care.

b. Restricting fluid intake to 1.5–2 L/day is reasonable in stage D if serum Na is low.

c. Modest exercise program benefits

i. Possible modest effects on all-cause hospitalization and all-cause mortality, CV death or CV hospitalization, and CV death or HF hospitalization

ii. Safe for patients with HF

d. Influenza, pneumococcal, and COVID-19 vaccines

e. Monitor and appropriately replace electrolytes (to minimize risk of arrhythmias).

f. Monitor for thyroid disease.

i. Hypothyroidism can be masked by HF symptoms.

ii. Hyperthyroidism will worsen systolic dysfunction.

g. Screen for and treat depression.

Patient Case

3. Which drug that J.T. (from Patient Case 2) is currently taking would be best to discontinue because of his HFrEF?

A. Acetaminophen.

B. Sertraline.

C. Cilostazol.

D. Levothyroxine.

C. HFpEF: Clinical evidence for efficacious agents for HFpEF has generally been disappointing. Therapies for symptoms, comorbidities, and risk factors that can worsen CVD are recommended.

1. SBP and diastolic blood pressure (DBP) should be well controlled (class 1 recommendation). HTN impairs myocardial relaxation and promotes cardiac hypertrophy.
2. Diuretics should be used for symptom relief in volume overload.
3. SGLT2 inhibitors can be beneficial to decrease HF hospitalizations and CV mortality (class 2a recommendation).
4. MRAs and ARNIs or ARBs may be considered to decrease HF hospitalizations, particularly among patients with LVEF on the lower end of the spectrum (class 2b recommendations) (TOPCAT, PARAGON-HF, CHARM-Preserved trials).
5. β-Blockers are not recommended for the management of HFpEF without other compelling indications (e.g., AF, MI) because of their association with a higher risk of HF hospitalizations).
6. Management of AF can be useful to improve symptomatic HF (class 2a recommendation).

D. HF with Mildly Reduced EF (HFmrEF)

1. Defined as HF with an LVEF of 41%–49% and evidence of spontaneous or provokable increased LV filling pressures (e.g., elevated natriuretic peptides, hemodynamic measurements)
2. Pharmacologic recommendations
   a. In patients with current or previous symptoms, use of an ARNI, ACE inhibitor, or ARB; MRA; and metoprolol succinate, carvedilol, or bisoprolol may be considered to reduce CV mortality and HF hospitalizations, particularly among patients with LVEF on the lower end of the spectrum (class 2b recommendation).
   b. SGLT2 inhibitors can be beneficial for decreasing CV mortality and HF hospitalizations (class 2a recommendation).

E. HFimpEF: HF with improved LVEF is defined as a documented LVEF of less than 40% at baseline plus a documented LVEF improvement of 10% or greater and a second LVEF measurement of greater than 40%.
   1. HFimpEF is distinct from both HFrEF and HFpEF because of distinct biology and improved outcomes compared with the other two causes.
   2. Guideline-directed medical therapy should not be discontinued in HFimpEF; discontinuation may cause HF recurrence (TRED-HF trial).

F. Medications That Cause/Exacerbate HF: An AHA scientific statement addresses medications that can cause or exacerbate HF. Drugs to avoid or use with caution in HF include:
   1. Drugs that promote sodium and water retention
      a. Nonsteroidal anti-inflammatory drugs (NSAIDs, including selective cyclooxygenase-2 inhibitors)
         i. Promote Na and water retention
         ii. Blunt diuretic response
         iii. Increase morbidity and mortality
      b. Corticosteroids
      c. Minoxidil
      d. Thiazolidinediones
   2. Drugs with negative inotropic effects
      a. Class I and III antiarrhythmic agents (except for amiodarone and dofetilide)
         i. Also have proarrhythmic effects
         ii. Amiodarone and dofetilide are safe in patients with HF.
         iii. Avoid dronedarone; it is contraindicated in patients with symptomatic HF with recent decompensation necessitating hospitalization or NYHA class IV HF.
      b. CCBs (except for amlodipine and felodipine)
         i. Also promote neurohormonal activation
         ii. Amlodipine and felodipine have been proven safe in patients with HF and can be added when additional BP reduction is needed; monitor for edema.
      c. Itraconazole
   3. Other
      a. Metformin: Increased risk of lactic acidosis (black box warning)
      b. Saxagliptin and alogliptin: Associated with increased risk of hospitalization
      c. Amphetamines (e.g., methylphenidate)
         i. α- and β-agonist activity
         ii. Cause tachycardia
         iii. Proarrhythmic effects
      d. Pregabalin
         i. Inhibits calcium channels
         ii. Lower-extremity edema, HF exacerbation
      e. Nutritional supplements
         i. Lack of evidence
         ii. Lack of product regulation
         iii. Potential for drug interactions and/or increased risk of bleeding
      f. Cilostazol: Proarrhythmic effects

II. ATRIAL FIBRILLATION

A. Background
   1. Prevalence
      a. Most common arrhythmia: 2.2 million Americans
      b. Prevalence increases with age.
      c. Common comorbidity in patients with valvular heart disease or HF
   2. Signs and symptoms
      a. Some patients have no symptoms.
      b. Potential symptoms that may be present to some degree include the following:
         i. Palpitations
         ii. Chest pain
         iii. Dyspnea
         iv. Fatigue
         v. Lightheadedness
      c. Rare cases of thromboembolic events
      d. Symptoms vary with ventricular rate, underlying LVEF, AF duration, and individual patient perceptions.
   3. Classification
      a. Paroxysmal: Spontaneous self-termination within 7 days of onset
      b. Persistent: Lasting more than 7 days
      c. Long-standing persistent: Continuous duration of more than 12 months
      d. Permanent: Present all the time, unable to return to SR using pharmacologic or nonpharmacologic options
      e. Nonvalvular: The absence of moderate-severe mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair

Patient Case

4. P.M. is a 52-year-old man (height 177.8 cm, weight 116 kg) with a history of HTN and a transient ischemic attack 2 years ago. He visits his primary care doctor with the chief concern of several weeks of a "fluttering" feeling in his chest on occasion. He thinks the fluttering is nothing; however, his wife insists he have it checked. His current medications include metoprolol tartrate 50 mg twice daily and aspirin 81 mg/day. He is adherent to this regimen and has health insurance, but he does not like to make the 3-hour trip to his primary care provider. His laboratory data from his past visit were all within normal limits. His vital signs today include BP 130/78 mm Hg and HR 76 beats/minute. All laboratory values are within normal limits. An electrocardiogram (ECG) reveals an irregularly irregular rhythm, with no P waves, and a HR of 74 beats/minute. A diagnosis of AF is made. What is the best approach for managing his AF at this time?

   A. Begin digoxin 0.25 mg/day.

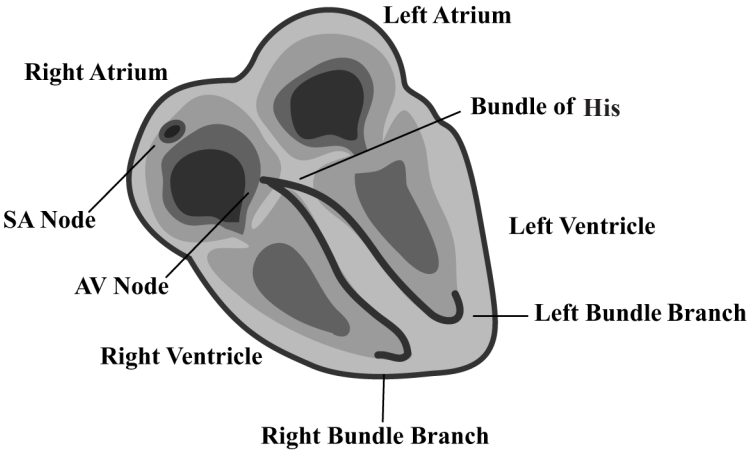
   B. Begin diltiazem CD 240 mg/day.

   C. Begin warfarin 5 mg/day and titrate to a goal INR of 2.5.

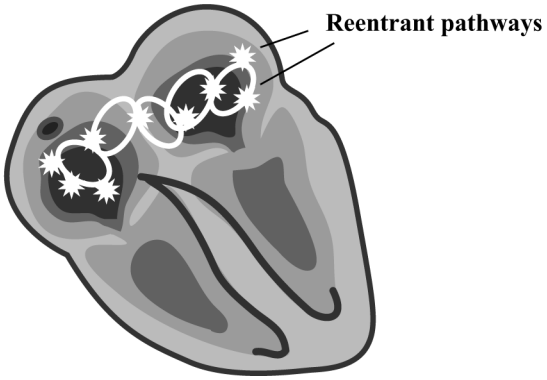
   D. Begin dabigatran 150 mg twice daily.

B. Pathophysiology

1. Cardiac conduction in a normal heart and a heart with atrial fibrillation (Figure 2)



The impulse:
1. Is generated by the SA node.
2. Propagates through atrial tissue.
3. Reaches the AV node.
4. Passes slowly through the AV node.
5. Travels through the bundle of His.
6. Is conducted simultaneously down the three bundle branches.
7. Is distributed to the ventricular tissue by small embedded Purkinje fibers.



The impulses:
1. Are generated in atrial tissues; ± focal activation, with reentry pathways
2. Bombard the AV node in a rapid and chaotic fashion.
3. Are propagated by the AV node after it repolarizes from the last impulse.
4. See 5–7 above.

Figure 2. Cardiac conduction and atrial fibrillation.
AV = atrioventricular; SA = sinoatrial.

2. ECG findings

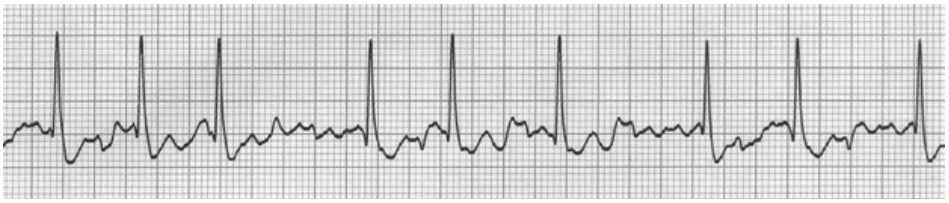


Figure 3. Electrocardiogram showing atrial fibrillation.

3. AF causes (Table 7).

Table 7. Potential Causes of AF

Atrial Distension	High Adrenergic Tone
Chronic hypertension	Alcohol withdrawal
Mitral valve disease	Thyrotoxicosis
Cardiomyopathy	Sepsis
Congenital defects	Binge drinking
Pulmonary hypertension	Surgery
Acute pulmonary embolus	Sympathomimetics such as cocaine or amphetamines
Myocardial ischemia	Excessive theophylline, caffeine
Sleep apnea	
Emphysema or other lung diseases	

C. Pharmacologic therapy
   1. Ventricular rate control
      a. If patients have a rapid ventricular rate, AV nodal blockade is necessary.
      b. Goal HR (resting HR less than 80 beats/minute) is reasonable in symptomatic patients (class IIa recommendation). A more lenient rate control (resting HR less than 110 beats/minute) may be reasonable in patients who are asymptomatic and have preserved ejection fraction (class IIb recommendation).
      c. The goal is to reduce symptoms and possibly prevent tachycardia-induced cardiomyopathy.
      d. Select the best agent according to individual clinical response and concomitant disease states.
         i. β-Blockers
            (a) Any agent with β-blockade can be used and dosed to the goal HR.
            (b) Labetalol or carvedilol may be preferred to non-DHP CCBs if additional α_1-blockade is desirable (e.g., HTN).
            (c) β-Blockers may be preferred in patients with a history of MI.
            (d) Select carvedilol, metoprolol succinate, or bisoprolol in patients with HFrEF
            (e) Avoid in patients with Wolff-Parkinson-White syndrome
            (f) Effective for controlling exercise-associated HR increases
         ii. Non-DHP CCBs: Verapamil or diltiazem
            (a) Avoid use if there is concomitant left ventricular systolic dysfunction.
            (b) May be preferred over β-blocker in patients with asthma or severe chronic obstructive pulmonary disease
            (c) Effective for controlling exercise-associated HR increases
            (d) Avoid in patients with Wolff-Parkinson-White syndrome
         iii. Digoxin
            (a) Often ineffective alone for controlling ventricular rate in AF, especially during exercise or movement (because of minimal effectiveness with sympathetic stimulation)
            (b) Not usually first-line therapy, especially when rapid rate control is desired (2014 AHA AF guidelines)
            (c) Can be included in regimen if patient has HFrEF
            (d) May be effective if additional HR control is needed when a patient is already receiving a β-blocker, diltiazem, or verapamil
            (e) Avoid in patients with Wolff-Parkinson-White syndrome
            (f) May be agent of choice if patient has uncontrolled HR and decompensated HF

iv. Amiodarone
(a) May be used for rate control in patients with HF who do not have an accessory pathway
(b) May be used for rate control in patients who are refractory to other therapies such as β-blockers, non-DHP CCBs, and digoxin

2. Rhythm control:
a. When to choose a rhythm-control approach
i. Historically, maintaining SR offered no advantage over ventricular rate control and was associated with more hospitalizations (AFFIRM trial).
ii. However, specific patients may benefit from a rhythm-control approach:
(a) Patients with intractable and intolerable symptoms such as dyspnea, palpitations, and exercise intolerance) despite adequate rate control
(b) Patients in whom adequate ventricular rate control cannot be achieved
iii. The EAST-AFNET 4 trial found rhythm control (with antiarrhythmics, cardioversion, or ablation) superior to rate control in reducing adverse CV outcomes among patients with a recent (less than 12 months prior) diagnosis of AF and concomitant CV conditions.
iv. The most recent AF guidelines were published before release of the EAST-AFNET 4 trial. Currently, it is reasonable to select an initial rhythm-control approach in selected patients with a recent (less than 12 months prior) diagnosis of AF and additional CV risk factors.

Table 8. Summary of the Pros and Cons of Rate Control vs. Rhythm Control

	Pros	Cons
Rate control strategy	Generally easy to achieve and maintain; out-of-hospital therapy typical	Electrical and structural remodeling because of continued AF makes future attainment of SR virtually impossible; safety not proven for younger patients
Rhythm control strategy	If patient is symptomatic with fatigue and exercise intolerance, these symptoms may improve if SR is attained (especially in patients with HF); minimizes development of structural atrial changes; acceptable for all age groups	Adverse effects of antiarrhythmic medications; cost of medications and monitoring; likelihood of AF recurrence; in-hospital stay may be necessary to initiate therapy

AF = atrial fibrillation; HF = heart failure; SR = sinus rhythm.

b. Cardioversion in AF
i. If cardioversion is attempted (electric or pharmacologic), the absence of atrial thrombi must be ensured.
ii. Without anticoagulation (thrombi caused by decreased or stagnant blood flow in the atria)
(a) AF for more than 48 hours = 15% rate of atrial thrombus.
(b) AF for more than 72 hours = 30% rate of atrial thrombus.
iii. Thrombi present plus cardioversion = 91% stroke rate.
iv. Ensure safe cardioversion by either:
(a) Transesophageal echocardiogram (TEE) to visualize the atria, *or*
(b) Three or more weeks of therapeutic anticoagulation
(1) INR 2.0-3.0 if warfarin is selected
(2) Direct oral anticoagulants (DOACs) may also be used
v. Continue anticoagulation for at least four weeks after cardioversion with either:
(a) Warfarin or
(b) DOAC

vi. Specific recommendations for anticoagulation are described in Table 9.

Table 9. Anticoagulation Strategies Surrounding Cardioversion of AF[a]

AF Type	Anticoagulation Recommendations
Unstable AF	• Synchronized cardioversion; anticoagulate immediately beforehand with parenteral therapy • Anticoagulate for ≥4 wk after cardioversion with warfarin or a DOAC if AF ≥ 48 hr or if duration is unknown
Stable AF, duration <48 hr[b]	ACCP (CHEST) guidelines: • Anticoagulate at presentation and continue through cardioversion – LMWH or UFH at full treatment doses • Anticoagulate for ≥4 wk afterward, regardless of baseline risk of stroke ACC/AHA/HRS AF guidelines: • Anticoagulation as soon as possible before cardioversion is recommended with a CHA_2DS_2-VASc score of ≥2 (men) or ≥3 (women); anticoagulation may be considered with a score of 0 or 1 (men) or 1 or 2 (women) – UFH, LMWH, or DOAC • Need for anticoagulation after cardioversion should be based on the patient's risk of thromboembolism, according to their CHA_2DS_2-VASc score
Stable AF, duration unknown or >48 hr (no TEE)	ACCP (CHEST) guidelines: • Anticoagulate for 3 wk before cardioversion – Warfarin with INR 2.0–3.0 or a DOAC • Anticoagulate for ≥4 wk afterward, regardless of baseline risk of stroke ACC/AHA/HRS AF guidelines: • Anticoagulate for ≥3 wk before cardioversion – Warfarin with INR 2.0–3.0, DOAC, or enoxaparin (full treatment doses) • Anticoagulate for 4 wk after cardioversion, regardless of CHA_2DS_2-VASc score
Stable AF, duration unknown or >48 hr (with TEE-guided cardioversion)	ACCP (CHEST) guidelines: • TEE-guided therapy with abbreviated anticoagulation before cardioversion – LMWH or UFH at full treatment doses should be initiated at the time of TEE, and cardioversion should be performed within 24 hr of TEE if no thrombus is seen • Anticoagulate for ≥4 wk after cardioversion, regardless of baseline risk of stroke ACC/AHA/HRS AF guidelines: • If no identifiable thrombus seen on TEE, cardioversion is reasonable, provided anticoagulation is achieved before TEE • If thrombus identified on TEE, 3 wk of therapeutic anticoagulation is required before cardioversion • Anticoagulation should be maintained after cardioversion for ≥4 wk

[a]Potential risk of cardioversion with antiarrhythmic drugs should be considered before treatment initiation.

[b]No randomized trials have compared different anticoagulation strategies in patients with AF < 48 hr.

ACC = American College of Cardiology; ACCP = American College of Chest Physicians; AF = atrial fibrillation; AHA = American Heart Association; DOAC = direct oral anticoagulant; HRS = Heart Rhythm Society; INR = international normalized ratio; LMWH = low-molecular-weight heparin; TEE = transesophageal echocardiography; UFH = unfractionated heparin.

January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Circulation 2019;140:e125-151; Lip GY, Banerjee A, Boriani G, et al. Antithrombotic therapy for atrial fibrillation: CHEST guideline and expert panel report. Chest 2018;151:1121-201.

c. Oral antiarrhythmic agents to induce or maintain SR (class Ic and class III agents are recommended in atrial fibrillation; choice of agent depends on patient comorbidities)
   i. Class Ic antiarrhythmics: 80% - 90% efficacy
      (a) Flecainide and propafenone can be considered first-line therapies for patients without structural heart disease (Figure 4). Propafenone also displays some nonselective β-blocking properties.
      (b) Concomitant AV nodal blocking agent (e.g., β-blocker or non-DHP CCB) typically required
      (c) Contraindicated in patients with structural heart disease (including CCD, HF, left ventricular hypertrophy, and valvular heart disease)
   ii. Class III antiarrhythmics
      (a) Amiodarone: 85%–95% efficacy
         (1) Has electrophysiologic properties of classes I–IV
         (2) Oral loading dose required (e.g., 400 mg 2 or 3 times per day for 2 weeks and then 400 mg/day for 4 weeks, followed by a 200-mg/day maintenance dose). Achieving a loading dose of 10 g is desirable. Many different regimens exist.
         (3) Long half-life of about 60 days
         (4) Has AV nodal blocking properties, which may help to control HR if AF recurs
         (5) May use in patients with HF
         (6) Hepatically metabolized: Cytochrome P450 (CYP) 3A4 substrate; inhibitor of CYP3A4, CYP1A2, CYP2C9, CYP2D6, and P-glycoprotein (P-gp)
         (7) Minimal incidence of ventricular arrhythmias
         (8) Drug interactions (many)
            (A) Digoxin: Increased digoxin exposure. Lower digoxin dose by 50%.
            (B) Warfarin: Increased warfarin exposure. Lower warfarin dose by 33%–50%.
            (C) Simvastatin: Increased simvastatin exposure. Do not exceed dose of simvastatin 20 mg/day.
            (D) Lovastatin: Increased lovastatin exposure. Do not exceed dose of lovastatin 40 mg/day.
            (E) β-Blockers, non-DHP CCBs, clonidine, ivabradine: Additive bradycardia
         (9) Extensive monitoring for noncardiac adverse effects
            (A) Liver function tests (LFTs): Baseline and every 6 months
            (B) Thyroid function tests: Baseline and every 6 months
            (C) Chest radiography: Baseline and annually
            (D) ECG: Periodically
            (E) Pulmonary function tests (including D_LCO [carbon dioxide diffusion in the lungs]): Baseline and for unexplained cough/dyspnea, chest radiographic abnormalities or clinical suspicion. Discontinue if pulmonary fibrosis occurs.
            (F) Ophthalmologic examination: Baseline (if visual impairment) and if patient has symptoms of visual impairment. Discontinue if optic neuritis occurs.
            (G) Skin toxicities: "Blue skin" syndrome and sunburn
            (H) Neurologic toxicity: Tremor, neuropathy
            (I) Nausea, vomiting
            (J) Adverse effects may require increased monitoring, dose reduction, or drug discontinuation

(b) Sotalol: 50%–60% efficacy
  (1) Renal excretion. Dose adjustment and vigilant corrected QT (QTc) interval monitoring necessary in renal impairment. Recommended starting dose is 80 mg twice daily (unless creatinine clearance [CrCl] less than 60 mL/minute, then 80 mg once daily).
  (2) Should be initiated in the hospital (minimum of 3-day stay), where QTc interval, serum electrolytes (e.g., K and magnesium), and renal function can be monitored
  (3) Contraindicated in patients with HF (stable or unstable); CrCl less than 40 mL/minute; QTc interval greater than 450 milliseconds; and second- or third-degree AV block or sick sinus syndrome (in absence of pacemaker)
  (4) Possesses nonselective β-blocking properties; may result in additive bradycardia with β-blockers, non-DHP CCBs, clonidine, ivabradine, and digoxin
  (5) Sotalol is ineffective for cardioversion but may be used for maintenance of NSR (normal SR).

(c) Dofetilide: 50%–60% efficacy
  (1) Should be initiated in the hospital (minimum of 3-day stay) so that QTc interval, serum electrolytes (e.g., K and magnesium), and renal function can be monitored
  (2) Starting dose is selected based on renal function
    (A) CrCl greater than 60 mL/minute: 500 mcg twice daily
    (B) CrCl 40–60 mL/minute: 250 mcg twice daily
    (C) CrCl 20–39 mL/minute: 125 mcg twice daily
    (D) CrCl less than 20 mL/minute: Contraindicated
  (3) Modification of subsequent doses is based on QTc interval measured 2–3 hours after initial dose: QTc > 500 milliseconds (or 550 milliseconds in ventricular conduction abnormalities) OR QTc increased greater than 15% above baseline: reduce dose by 50%
  (4) If QTc is greater than 500 milliseconds (or 550 milliseconds in ventricular conduction abnormalities) at any point after in-hospital doses 2–5, discontinue dofetilide
  (5) Hepatically metabolized by CYP3A4
  (6) Renal elimination through renal cationic secretion; check QTc interval if renal function declines
  (7) Contraindicated in patients with CrCl less than 20 mL/minute or QTc interval greater than 440 milliseconds (or 500 milliseconds for patients with ventricular conduction abnormalities)
  (8) May use in patients with HF
  (9) Drug interactions
    (A) Avoid concomitant use of the following drugs: cimetidine, verapamil, itraconazole, ketoconazole, hydrochlorothiazide, prochlorperazine, megestrol, dolutegravir, and trimethoprim alone or in combination with sulfamethoxazole
    (B) Use CYP3A4 inhibitors, triamterene, metformin, and amiloride with caution: increased dofetilide exposure

(d) Dronedarone: 21%–25% efficacy
  (1) Amiodarone analog lacking the iodine moiety that contributes to the thyroid toxicity of amiodarone
  (2) Has electrophysiologic properties of classes I–IV
  (3) Dose: 400 mg twice daily with morning and evening meal
  (4) Hepatically metabolized; CYP3A4 substrate; CYP3A4, CYP2D6, and P-gp inhibitor
  (5) Half-life is 13–19 hours.
  (6) Small increase in SCr by 0.1 mg/dL may be seen, probably a result of inhibition of creatinine's tubular secretion; rapid onset, will plateau after 7 days, and is reversible. Monitor SCr periodically.

(7) Acute kidney injury has also been reported, and it is usually reversible with drug discontinuation.
(8) Contraindicated in permanent AF; NYHA class II or III HF with recent decompensation necessitating hospitalization; NYHA class IV HF; second- or third-degree AV block or sick sinus syndrome (in absence of pacemaker); severe liver impairment, HR less than 50 beats/minute; concurrent use of strong CYP3A4 inhibitors or QTc interval–prolonging agents; history of amiodarone-induced hepatotoxicity or pulmonary toxicity; pregnancy; or QTc interval 500 milliseconds or greater
(9) One trial found dronedarone less effective than amiodarone for the maintenance of SR, but with fewer adverse effects.
(10) Drug interactions
    (A) Digoxin: Increased digoxin exposure; lower digoxin dose by 50%
    (B) β-Blockers, non-DHP CCBs, and clonidine: Excessive bradycardia; initiate these drugs at lowest dose. Diltiazem and verapamil can increase dronedarone exposure; therefore, monitor ECG.
    (C) Statins: Increased statin exposure. Limit dose of simvastatin to 10 mg/day and lovastatin to 20 mg/day.
    (D) Dabigatran: Dronedarone increases dabigatran exposure in patients with renal impairment; decrease dabigatran dose to 75 mg twice daily in patients with moderate renal impairment (CrCl 30–50 mL/minute), and avoid coadministration with CrCl less than 30 mL/minute.
    (E) Strong CYP3A4 inhibitors and inducers: Avoid.
    (F) Cyclosporine, tacrolimus, sirolimus: Increased exposure of these agents; monitor serum concentrations closely
(11) Other safety issues
    (A) Liver injury: According to postmarketing surveillance, dronedarone has been associated with rare but severe hepatic liver injury. Hepatic enzymes should be monitored, especially during the first 6 months of treatment.
    (B) Pulmonary toxicity: In postmarketing surveillance, cases of interstitial lung disease, including pneumonitis and pulmonary fibrosis, have been reported. Patients should report any new signs of dyspnea or nonproductive cough.

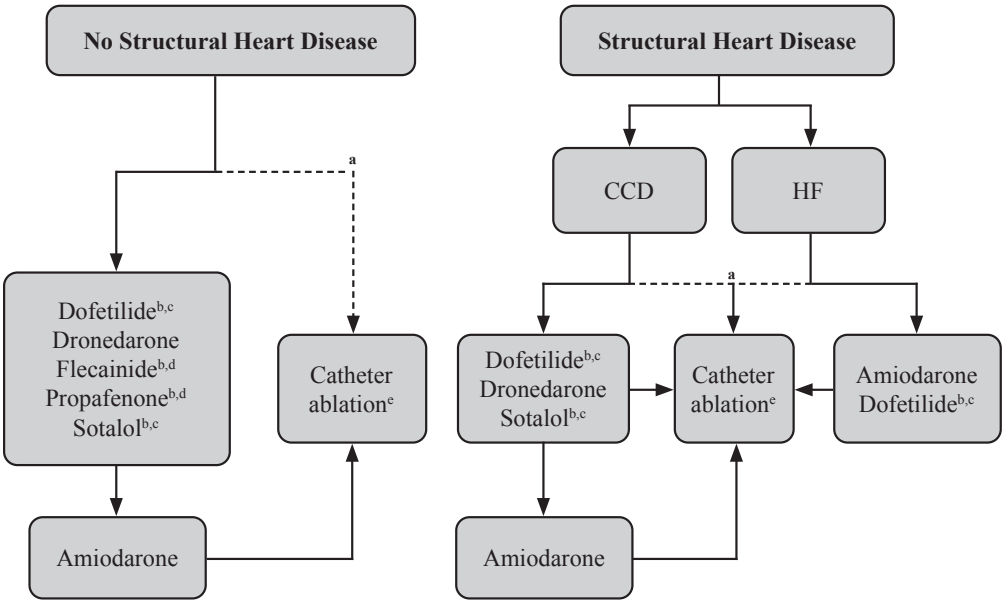


Figure 4. Options for rhythm control in patients with paroxysmal and persistent atrial fibrillation. Antiarrhythmics are listed in alphabetical order and not order of preference

[a]Depends on patient preference when performed in experienced centers.

[b]Not recommended with severe left ventricular hypertrophy (wall thickness > 1.5 cm).

[c]Use with caution in patients at risk of torsades de pointes ventricular tachycardia.

[d]Should be combined with atrioventricular nodal blocking agents.

[e]Catheter ablation is only recommended as first-line therapy for patients with paroxysmal atrial fibrillation (class IIa recommendation).

CCD = chronic coronary disease; HF = heart failure.

Adapted with permission from: January CT, Wann SL, Sacco RL, et al. AHA/ACC/HRS guideline for the management of patients with atrial fibrillation. Executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and Heart Rhythm Society. Circulation 2014;130:2071.

3. Antithrombotic therapy
    a. The average annual stroke rate is 5% per year without anticoagulation.
        i. A patient's individual risk can vary from about 1% to 20% per year depending on risk factors.
        ii. This risk is independent of current cardiac status (i.e., SR or AF).
    b. Risk stratification and treatment determination is based on the CHA_2DS_2-VASc score (Tables 10–11). Of note, the 2018 CHEST guidelines for anticoagulation in atrial fibrillation no longer recommend antiplatelet therapy alone for prevention of stroke or systemic embolism.

Table 10. Risk Stratification for Antithrombotic Therapy Using the CHA_2DS_2-VASc Score[a]

Risk Factor	Score
CHF or LVEF ≤ 40%	1
Hypertension	1
Age ≥ 75 yr	2
Diabetes	1
Stroke, TIA, thromboembolism	2
Vascular disease	1
Age 65–74 yr	1
Sex category (female)	1

[a]For use in patients with nonvalvular atrial fibrillation. Maximum point value is 9.

CHF = congestive heart failure; LVEF = left ventricular ejection fraction; TIA = transient ischemic attack.

Table 11. AHA/ACC/HRS Guideline Recommendations for Antithrombotic Therapy in Patients with Nonvalvular Atrial Fibrillation per CHA_2DS_2-VASc Score

CHA_2DS_2-VASc Score = 0 in Men or 1 in Women	CHA_2DS_2-VASc Score = 1 in Men or 2 in Women	CHA_2DS_2-VASc Score = 2 in Men or 3 in Women
Reasonable to omit anticoagulant therapy	May consider oral anticoagulation	Oral anticoagulant therapy is indicated. DOAC over warfarin in patients eligible for DOACs[a]

[a]Exclusions include moderate to severe mitral stenosis or mechanical heart valve.

DOAC = direct oral anticoagulant.

Patient Case

5. H.D. is a 67-year-old man with a history of HTN and AF for 4 years. His medications include ramipril 5 mg twice daily, sotalol 120 mg twice daily, digoxin 0.125 mg/day, and warfarin 5 mg/day. He visits his primary care physician after being discharged from the emergency department with increased fatigue on exertion palpitations, and lower extremity edema. His vital signs today include BP 115/70 mm Hg and HR 88 beats/minute, and all laboratory results are within normal limits; however, his lower extremity edema has worsened. His INR is 2.8. His ECG shows AF. An echocardiogram reveals an LVEF of 35%–40%. H.D.'s physician would like to continue a rhythm control approach. What is the best treatment option for managing his AF?
   A. Discontinue sotalol and begin metoprolol succinate 12.5 mg/day.
   B. Discontinue sotalol and begin dronedarone 400 mg twice daily.
   C. Discontinue sotalol and begin amiodarone 400 mg twice daily, tapering to goal dose of 200 mg/day for the next 6 weeks.
   D. Continue sotalol and add metoprolol tartrate 25 mg twice daily.

D. Nonpharmacologic therapies (procedures)
   1. Electrical cardioversion (low-energy cardioversion; sedation highly desirable)
   2. AV nodal ablation: Ablate AV node and chronically pace the ventricles.
   3. Pulmonary vein ablation: Ablates the origin of the abnormal atrial foci, which is often near the pulmonary vein–atrial tissue intersection.

III. HYPERTENSION

Definition: HTN is a persistent, nonphysiologic elevation of BP; it is defined as an SBP of 130 mm Hg or greater and/or a DBP of 80 mm Hg or greater.

A. Background
   1. Prevalence
      a. Most common chronic disease in the United States
      b. Affects 46% of the population
      c. Prevalence increases with age
      d. Major modifiable risk factor for CVD and stroke
   2. Etiology
      a. Essential HTN: 90% (no identifiable cause)
         i. Obesity is a contributor
         ii. Evaluate Na intake

   b. Secondary HTN
      i. Primary aldosteronism
      ii. Renal parenchymal disease
      iii. Renal artery stenosis
      iv. Obstructive sleep apnea
      v. Cushing syndrome
      vi. Thyroid or parathyroid disease
      vii. Medications (e.g., cyclosporine, NSAIDs, sympathomimetics)
      viii. Pheochromocytoma
3. Diagnosis
   a. Periodic screening for all people older than 18 years
   b. Patient should be seated quietly in chair for at least 5 minutes.
   c. Use appropriate cuff size (bladder length at least 80% the circumference of the arm).
   d. Take BP at least twice, separated by at least 2 minutes.
   e. The average BP on two separate visits is required to diagnose HTN accurately.
   f. Home blood pressure monitoring (HBPM) and ambulatory blood pressure monitoring (ABPM) are recommended to confirm diagnosis, screen for white-coat HTN, and screen for masked HTN
      i. White-coat HTN: Office blood pressure is 130/80-160/100 mm Hg after a 3-month trial of lifestyle modification but with daytime ABPM or HBPM blood pressure less than 130/80 mm Hg
      ii. Masked HTN: Office blood pressure is 120-129/less than 80 mm Hg after a 3-month trial of lifestyle modification; daytime ABPM or HBPM blood pressure of 130/80 mm Hg or greater
4. Benefits of treating elevated BP
   a. Decreased risk of stroke (by 35-40%)
   b. Decreased risk of MI (by 20-25%)
   c. Decreased risk of HF (by 50%)
5. Effects of lifestyle modifications on BP (Table 12)

Table 12. Recommended Lifestyle Modifications

Modification	Recommendation	Approximate SBP Reduction
Weight reduction	Maintain a normal body weight (BMI 18.5–24.9 kg/m^2)	5–20 mm Hg per 10-kg weight loss
Adopt DASH eating plan (includes substantial K intake)	Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat	8–14 mm Hg
Reduce Na intake	Reduce Na intake to < 1500 mg/day Reducing Na intake by at least 1000 mg/day will lower BP if desired daily Na intake goal is not achieved	2–8 mm Hg
Physical activity	Engage in regular aerobic physical activity such as brisk walking (at least 30 min/day most days of the week)	4–9 mm Hg
Moderation of alcohol consumption	Limit consumption to: Women and those of lower body weight: 1 drink/day (12 oz of beer, 5 oz of wine, or 1.5 oz of 80-proof whiskey) Men: 2 drinks/day	2–4 mm Hg

BMI = body mass index; BP = blood pressure; DASH = Dietary Approaches to Stop Hypertension; Na = sodium; SBP = systolic blood pressure.

B. Therapeutic management
   1. Patient classification and management in adults (Table 13)

Table 13. Classification of BP and Hypertension and Lifestyle Modification Recommendations

BP Classification	SBP (mm Hg)		DBP (mm Hg)
Normal	< 120	*and*	< 80
Elevated	120-129	*and*	< 80
Stage 1 hypertension	130-139	*or*	80-89
Stage 2 hypertension	≥140	*or*	≥ 90
Hypertensive urgency/ emergency	>180	*or*	>120

BP = blood pressure; DBP = diastolic blood pressure; SBP = systolic blood pressure

Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/ American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2018;71:e127-248.

Patient Cases

6. W.D. is a 55-year-old woman who was recently admitted to the hospital with acute myocardial infarction which was treated with a stent. She has a medical history of HTN and GERD. She is visiting your clinic today for management of her cardiovascular medications. Her vitals today include BP 152/86 mm Hg and HR 82 beats/minute. Her labs are all WNL, including Na 140 mEq/L, K 4.3 mEq/L, and SCr 1.0 mg/dL. Her current medication regimen includes clopidogrel 75 mg daily, aspirin 81 mg daily, and atorvastatin 40 mg daily. What is the most appropriate approach to manage her HTN?
   A. Add carvedilol monotherapy
   B. Add lisinopril and metoprolol
   C. Add amlodipine and metoprolol
   D. Add lisinopril monotherapy

7. T.J. is a 58-year-old African American woman presenting for routine follow-up of her chronic obstructive pulmonary disease. She has no other medical history. Her blood pressure today (average of 2 readings) is 138/88 mm Hg. Her HR is 77 beats/minute. Her BP at her last visit was 136/86 mm Hg. Her current medications include tiotropium dry powder inhaler daily and an albuterol metered dose inhaler as needed. Her labs include Na 140 mEq/L, K 4.0 mEq/L, Cl 102 mEq/L, bicarbonate 28 mEq/L, serum urea nitrogen 14 mg/dL, and SCr 0.8 mg/dL. Her 10-year ASCVD risk is 12%. What is the best approach for managing her HTN?
   A. Begin diet and lifestyle modifications only
   B. Begin lifestyle modifications and add amlodipine 5 mg daily
   C. Begin lifestyle modifications and add lisinopril 2.5 mg daily
   D. Begin lifestyle modifications and add lisinopril 2.5 mg daily plus hydrochlorothiazide 12.5 mg daily

2. The 2017 ACC/AHA guideline blood pressure thresholds and goals are listed in Table 14.

Table 14. BP Thresholds for Goals of Pharmacologic Therapy in Patients with HTN According to Clinical Condition

Clinical Condition	BP Threshold, mm Hg	BP Goal, mm Hg
Clinical CVD or 10-year ASCVD risk ≥10%	≥130/80	<130/80 for all
No clinical CVD and 10-year ASCVD risk <10%	≥140/90	
Diabetes[a]	≥130/80	
Chronic kidney disease	≥130/80	
Chronic kidney disease after renal transplantation	≥130/80	
Heart failure	≥130/80	
Stable ischemic heart disease	≥130/80	
Secondary stroke prevention	≥140/90	
Secondary stroke prevention (lacunar)	≥130/80	
Peripheral arterial disease	≥130/80	
Older persons (≥65 years; noninstitutionalized, ambulatory, community-living)	≥130 (SBP)	<130 (SBP)

[a]According to the 2017 ACC/AHA HTN guideline.

ASCVD = atherosclerotic cardiovascular disease; BP = blood pressure; CVD = cardiovascular disease; SBP = systolic blood pressure.

3. Blood pressure treatment strategies according to BP (in mm Hg) and ASCVD risk are located in Figure 5.

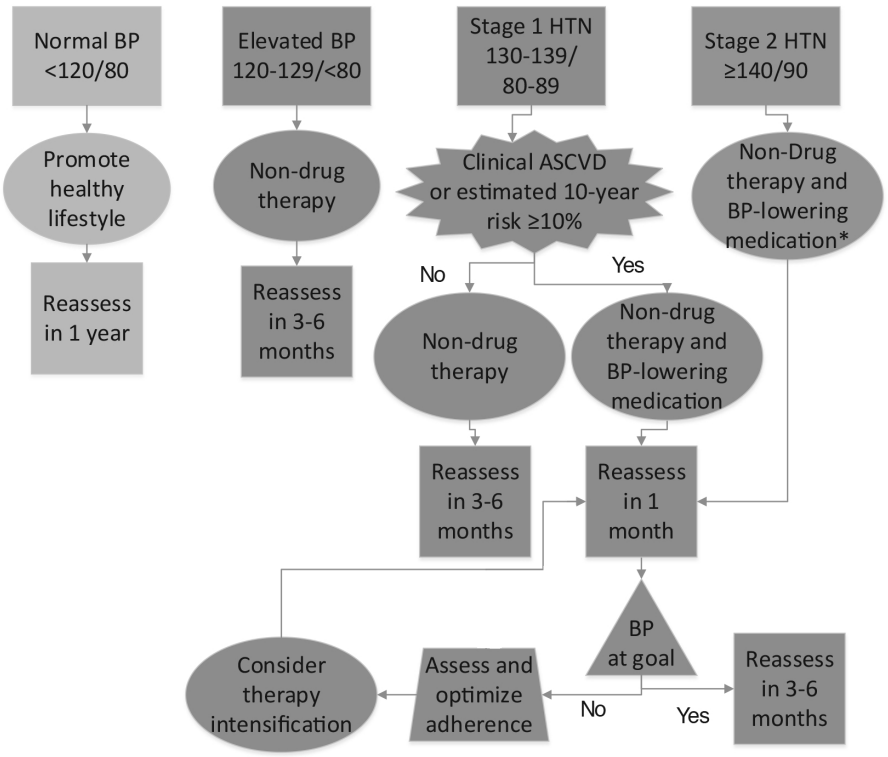


Figure 5. BP treatment strategies according to BP level and ASCVD risk.

*Initiation of antihypertensive drug therapy with two first-line agents of different classes, either as separate agents or in a fixed-dose combination, is recommended in adults with stage 2 HTN and an average blood pressure of greater than 20/10 mm Hg above their blood pressure target.

ASCVD = atherosclerotic cardiovascular disease; BP = blood pressure.

Adapted from: McConnell KJ. Blood pressure management of adult patients. In: Baker WL, Beavers C, Bolesta S, et al., eds. ACCP/ASHP 2019 Cardiology Pharmacy Preparatory Review and Recertification Course, 2019. Lenexa, KS: American College of Clinical Pharmacy, 2019:95.

4. Select an appropriate drug therapy regimen
    a. Initiating therapy with a single antihypertensive drug is reasonable in adults with stage 1 HTN and a BP goal of less than 130/80 mm Hg
    b. Initiating antihypertensive drug therapy with two first-line agents of different classes is recommended in adults with stage 2 HTN and an average BP greater than 20/10 mm Hg above their BP target
    c. First-line agents include thiazide diuretics, CCBs, and ACE inhibitors or ARBs.
    d. First-line agents for patients with comorbidities are described in Figure 6.

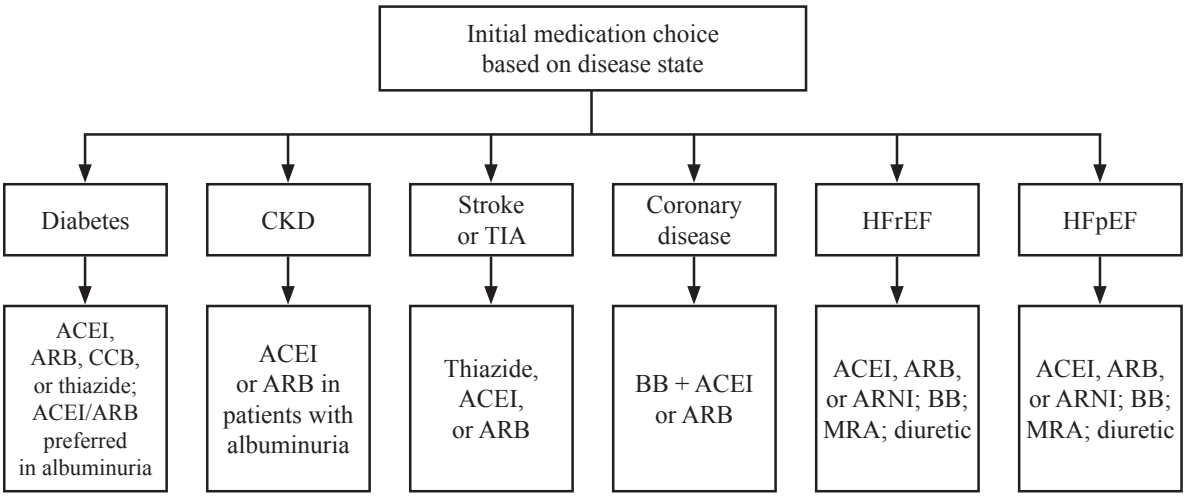

Initial medication choice based on disease state
Diabetes
CKD
Stroke or TIA
Coronary disease
HFrEF
HFpEF
ACEI, ARB, CCB, or thiazide; ACEI/ARB preferred in albuminuria
ACEI or ARB in patients with albuminuria
Thiazide, ACEI, or ARB
BB + ACEI or ARB
ACEI, ARB, or ARNI; BB; MRA; diuretic
ACEI, ARB, or ARNI; BB; MRA; diuretic

Figure 6. Selecting appropriate therapy for hypertension on the basis of disease state.

AA = aldosterone antagonist; ACEI = angiotensin-receptor converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor–neprilysin inhibitor; BB = β-blocker; CCB = calcium channel blocker; CKD = chronic kidney disease; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; MRA = mineralocorticoid receptor antagonist; TIA = transient ischemic attack.

5. Considerations with specific antihypertensive agents
    a. β-Blockers
        i. Evidence is insufficient to recommend β-blockers as initial therapy in patients without specific CV comorbidities.
        ii. Caution with asthma or severe chronic obstructive pulmonary disease (especially higher doses) because of pulmonary β-receptor blockade, especially with nonselective β-blockers or high-dose selective β-blockers.
        iii. Greater risk of developing diabetes than with an ACE inhibitor, ARB, and CCB; use caution in patients at high risk of diabetes (e.g., family history, obesity)
        iv. Can mask some signs of hypoglycemia in patients with diabetes
        v. Can cause depression
    b. Thiazides
        i. Can worsen gout by increasing serum uric acid
        ii. May have reduced efficacy in severely impaired renal function
        iii. Greater risk of developing diabetes than with ACE inhibitor, ARB, and CCB; use caution in patients at high risk of diabetes (e.g., family history, obesity)
        iv. Can assist in the management of osteoporosis by preventing urine calcium loss
        v. Monitor for hyponatremia and hypokalemia.
    c. ACE inhibitors and ARBs
        i. Contraindicated in pregnancy
        ii. Contraindicated with bilateral renal artery stenosis

iii. Monitor K closely, especially if renal impairment exists or another K-sparing drug or K supplement is used.

d. Direct renin antagonist (aliskiren)
   i. Not recommended as first-line HTN therapy
   ii. Avoid concurrent use with ACE inhibitors or ARBs in patients with renal impairment (CrCl less than 60 mL/minute).
   iii. Contraindicated in pregnancy
   iv. Contraindicated in patients with diabetes when used in combination with ACE inhibitors or ARBs because of increased risk of renal impairment, hyperkalemia, and hypotension
   v. Avoid use in combination with cyclosporine or itraconazole.

e. Calcium channel blockers
   i. Dihydropyridine CCBs
      (a) Amlodipine, felodipine, nifedipine
      (b) Monitor for peripheral edema, reflex tachycardia, and orthostatic hypotension
      (c) Useful for isolated systolic hypertension
   ii. Nondihydropyridine CCBs
      (a) Diltiazem, verapamil
      (b) Indicated in hypertensive patients with comorbid conditions which would benefit from HR reduction (e.g., atrial fibrillation, stable angina)
      (c) Contraindicated in heart block and sick sinus syndrome
      (d) Potential drug interactions due to CYP450 inhibition

6. Considerations within specific patient populations
   a. Patients with CCD: Potent vasodilators (hydralazine, minoxidil, and DHP CCBs) may cause reflex tachycardia, thereby increasing myocardial oxygen demand; can attenuate this by also using an AV nodal blocker (β-blocker or non-DHP CCB)
   b. Older adult patients (65 and older):
      i. Treatment of HTN with an SBP treatment goal of less than 130 mm Hg is recommended for noninstitutionalized ambulatory community-dwelling adults with an average SBP of 130 mm Hg or greater
      ii. For older adults with HTN and a high burden of comorbidity and limited life expectancy, clinical judgment, patient preference, and a team-based approach to assess risk-benefit is reasonable for decisions regarding intensity of blood pressure lowering and choice of antihypertensives
      iii. The SPRINT trial published in late 2015 showed that targeting an SBP of less than 120 mm Hg, compared with less than 140 mm Hg, resulted in lower rates of fatal and nonfatal major CV events and death from any cause among patients at high risk of CV events but without diabetes. Twenty-five percent of the study population was older than 75 years.
      iv. Caution with antihypertensive agents and orthostatic hypotension
   c. Black patients: Although data regarding race-based differences in treatment responses are controversial and falling out of favor, guidelines still recommend preferential use of thiazide-type diuretics or CCBs in the absence of compelling indications for other drug classes.
   d. Women
      i. Estrogen-containing contraceptives can increase BP, and the risk can increase with the duration of use.
      ii. HTN increases the risk to mother and fetus in women who are pregnant. Preferred medications include methyldopa, nifedipine, and labetalol. ACE inhibitors, ARBs, and aliskiren should not be used because of the potential for fetal defects.

7. Monitoring
   a. Have the patient return in 4 weeks to assess efficacy (sooner if clinically indicated).

b. If there is an inadequate response with the first agent with optimal dosing (and adherence is verified) and no compelling indication exists, initiate therapy with a drug from a different class while continuing initial therapy.

8. Resistant HTN
   a. Confirm diagnosis
      i. Office BP of 130/80 mm Hg or greater *and* patient taking at least three antihypertensive medications at optimal doses, including a diuretic (confirmed adherence) *OR*
      ii. Office BP of <130/80 mm Hg but patient requires at least four antihypertensive medications
   b. Exclude pseudoresistance
      i. Ensure accurate office BP readings
      ii. Exclude white-coat HTN
      iii. Ensure adherence
   c. Identify and reverse contributing factors
      i. Lifestyle factors
         (a) Obesity
         (b) High-salt, low-fiber diet
         (c) Physical inactivity
         (d) Excessive alcohol use
      ii. Interfering medications
         (a) NSAIDs
         (b) Sympathomimetics
         (c) Stimulants
         (d) Oral contraceptives
   d. Screen and treat for secondary causes of HTN (described earlier)
   e. Assess for target organ damage
   f. Pharmacological treatment
      i. Maximize diuretic therapy
         (a) Use thiazide or thiazide-like diuretics if eGFR > 25-30 mL/min/m^2
            (1) Chlorthalidone and indapamide have the most evidence for reducing cardiovascular outcomes
            (2) Chlorthalidone is more effective at inducing predictable natriuresis in patients with an eGFR 30-45 mL/min/m^2
         (b) Use loop diuretics if eGFR < 30 mL/min/m^2
      ii. Add MRA (spironolactone or eplerenone)
      iii. Alter dosing times to include a nocturnal dose or divide doses of drugs with half-lives <12-15 hours
      iv. Add other agents from different drug classes
      v. Addition of hydralazine or minoxidil requires concomitant use of a ß-blocker and diuretic
   g. Follow-up
      i. Ensure attainment of target BP after six months of therapy
      ii. If patient not at goal, refer to appropriate specialists

IV. DYSLIPIDEMIA

A. The AHA/ACC released updated Cholesterol Guidelines in 2018 in conjunction with 10 other organizations. Major changes in new guidelines:
   1. Emphasis on personalized risk assessment and shared decision making using tools listed in (D) below
   2. Re-introduction of LDL-C and non-HDL-C goals
   3. Recommendations for statin and nonstatin therapies

B. Goals of Therapy
   1. Reduce CV morbidity and mortality
   2. Achieve LDL-C goals, when appropriate

C. Nonpharmacologic recommendations
   1. Lifestyle modification is cornerstone of initial intervention
   2. Heart-healthy diet
      a. Recommend healthy diets such as the Dietary Approaches to Stop Hypertension (DASH) diet or the Mediterranean Diet
      b. Emphasize consumption of fruits, vegetables, whole grains, low-fat dairy products, skinless poultry and fish, nuts and legumes, and nontropical vegetable oils
      c. Limit sweets, sugar-sweetened beverages, and red meats
      d. Lower intake of saturated fats and replace with unsaturated fats (especially polyunsaturated fats)
   3. Regular exercise
   4. Engage in moderate-to-vigorous intensity aerobic physical activity 3-4 times per week for an average of 40 minutes per session
   5. Smoking cessation

D. Pharmacologic recommendations
   1. Therapy recommendations are divided into patient management groups:
      a. Secondary ASCVD prevention
      b. Severe hypercholesterolemia (LDL-C ≥190 mg/dL)
      c. Diabetes
      d. Primary prevention
   2. Pharmacologic management of dyslipidemia is detailed in Figure 7, and general principles are described below:
      a. First, initiate statin therapy if indicated. Optimize statin therapy (high intensity or maximally tolerated dose) before adding nonstatin therapy
      b. Second, consider nonstatin therapy if additional LDL lowering is warranted.
      c. According to the 2018 ACC/AHA management of blood cholesterol guidelines, ezetimibe should generally be the first nonstatin therapy considered, followed by the addition of a proprotein convertase subtilisin/kexin type 9 serine protease (PCSK9) monoclonal antibody (mAb) in selected patient groups (Figure 7).
      d. Of note, the 2022 ACC expert consensus pathway provides alternative recommendations.
         i. Either ezetimibe or PCSK9 mAbs may be considered as first-line adjunctive therapy to maximally tolerated statin therapy for patients with known ASCVD or baseline LDL of 190 mg/dL or greater. PCSK9 mAbs may be preferred in patients who require greater than 25% additional LDL lowering.
         ii. If further LDL lowering is warranted, the addition of the other nonstatin agent (ezetimibe or PCSK9 mAb) may be considered second.
         iii. If a third nonstatin therapy is warranted, the addition of bempedoic acid or the replacement of a PCSK9 mAb with inclisiran may be considered.
   3. Special populations
      a. Patients age >75 years
         i. Reasonable to initiate a moderate-intensity statin or continue a moderate- or high-intensity statin if benefits outweigh risks
         ii. Reasonable to discontinue statin therapy if patients have functional decline, multimorbidity, frailty, or reduced life expectancy limits potential benefits

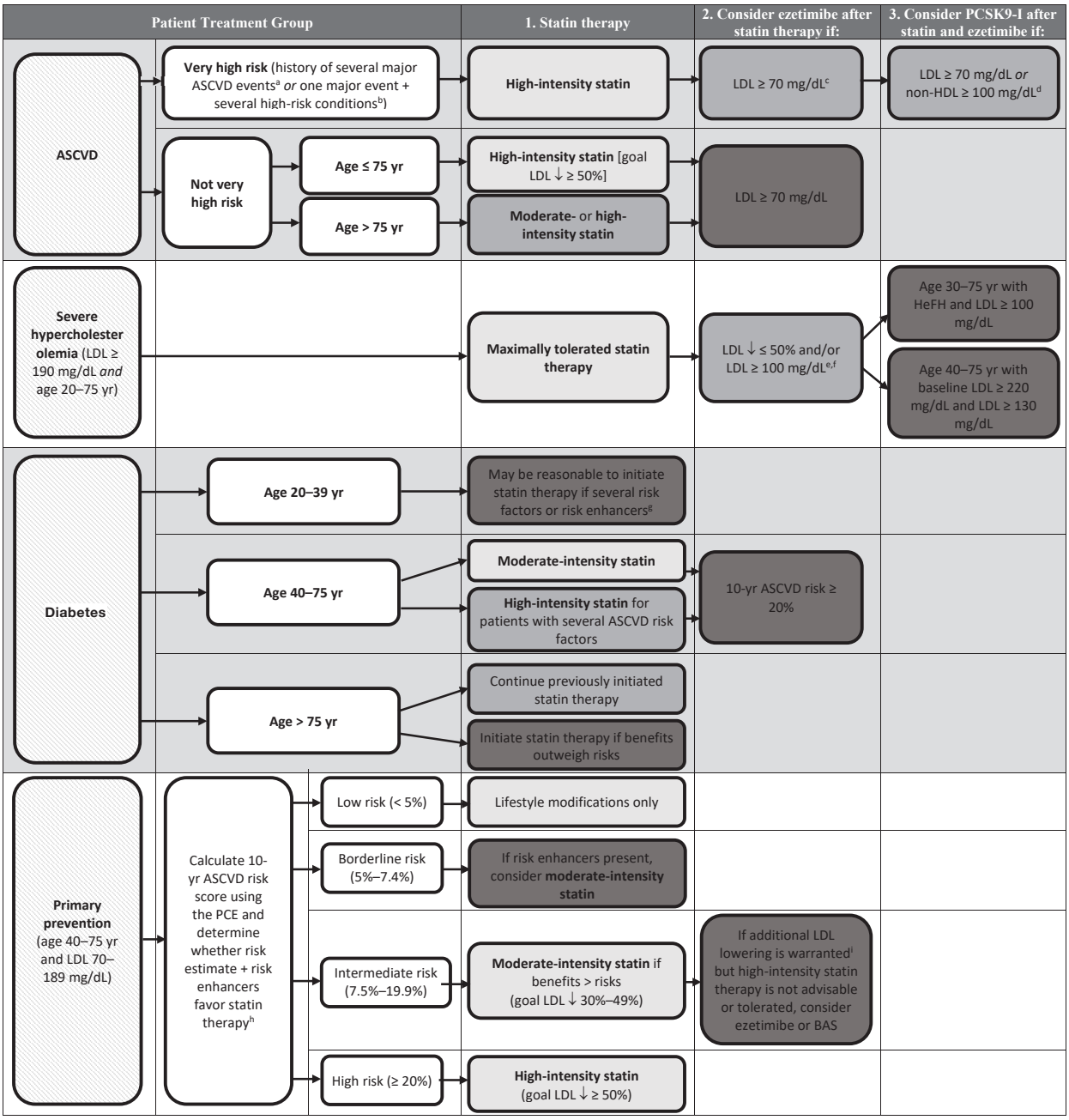


Figure 7. Statin and nonstatin therapy recommendations according to patient treatment group.
Key: Class I (strong) recommendation.
Class IIa (moderate) recommendation; therapy is reasonable.
Class IIb (weak) recommendation; therapy may be considered.

[a]Major ASCVD events are acute coronary syndrome (ACS) within the past 12 mo, other history of myocardial infarction (MI), history of ischemic stroke, and symptomatic peripheral artery disease.

[b]High-risk conditions are age ≥ 65 yr, HeFH, history of coronary artery bypass surgery or percutaneous coronary intervention outside the major ASCVD event(s), diabetes, hypertension, chronic kidney disease (eGFR 15–59 mL/min/1.73 m^2), current smoking, history of congestive heart failure, and persistently elevated LDL ≥ 100 mg/dL despite maximally tolerated statin therapy and ezetimibe.

[c]The 2022 ACC expert consensus pathway on nonstatin therapy suggests a target LDL reduction ≥ 50% and LDL < 55 mg/dL.

[d]Clinical evidence supports adding a PCSK9 inhibitor after maximally tolerated statin therapy, but adding ezetimibe first is more cost-effective.

(Footnotes are continued on the next page)

[e]The 2022 ACC expert consensus pathway on nonstatin therapy suggests a target LDL reduction ≥ 50% and LDL < 70 mg/dL for patients with clinical ASCVD without FH and a target LDL reduction ≥ 50% and LDL < 55 mg/dL for patients with clinical ASCVD and FH.

[f]May consider adding a BAS to statin and ezetimibe if LDL reduction is < 50% and fasting TG ≤ 300 mg/dL, especially if ineligible for PCSK9 inhibitor therapy.

[g]Diabetes-specific risk enhancers include diabetes of long duration (≥ 10 yr with type 2 diabetes or ≥ 20 yr with type 1 diabetes); microvascular complications (albuminuria [≥ 30 mcg/mg creatinine]), eGFR < 60 mL/min/1.73 m^2, retinopathy, or neuropathy; or ankle-brachial index < 0.9.

[h]If risk decision is uncertain (especially in patients with borderline and intermediate risk), consider measuring coronary artery calcium.

[i]The 2022 ACC expert consensus pathway on nonstatin therapy suggests a target of LDL reduction ≥ 50% and LDL < 70 mg/dL.

ASCVD = atherosclerotic cardiovascular disease; BAS = bile acid sequestrant; HeFH = heterozygous familial hypercholesterolemia; PCE = pooled cohort equation; PCSK9 = proprotein convertase subtilisin kexin/type 9 serine protease.

Information from: Grundy SM, Stone NJ, Bailey AL, et al. 2018 ACC/AHA/AACVPR/AAPA/ABC/ACPM/ADA/AGS/ APhA/ASPC/NLA/ PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2019;139:e1082-43; Lloyd-Jones D, Morris P, Ballantyne CM, et al. 2022 ACC expert consensus decision pathway on the role of nonstatin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk. J Am Coll Cardiol 2022;80:1366-418.

b. Hypertriglyceridemia
   i. Primary goal is to prevent pancreatitis
   ii. Evaluate for secondary causes (Table 15)

Table 15. Common Secondary Causes of Elevated LDL-C and TG

Cause	Increase LDL-C	Increase TG
Medications	Amiodarone, cyclosporine, diuretics, glucocorticoids	Anabolic steroids, atypical antipsychotics, β-blockers, bile acid sequestrants, glucocorticoids, hormone therapy, protease inhibitors, raloxifine, retinoic acid, sirolimus, tamoxifen, thiazides
Dietary influences	Saturated or *trans* fats, weight gain, anorexia	Very low-fat diets, high carbohydrate intake (refined), excess alcohol, weight gain
Disease states and medical conditions	Nephrotic syndrome, biliary obstruction, hypothyroidism, obesity, pregnancy	Poorly controlled diabetes, hypothyroidism, obesity, pregnancy, nephrotic syndrome, chronic renal failure, lipodystrophies

LDL-C = low-density lipoprotein cholesterol; TG = triglycerides.

   iii. Moderate hypertriglyceridemia (triglycerides [TG] 175-499 mg/dL)
      (a) Address and treat lifestyle factors, comorbidities, and medications which increase TGs
      (b) If persistently elevated and ASCVD risk ≥7.5%, consider initiation or intensification of statin therapy
   iv. Severe hypertriglyceridemia (TG ≥ 500 mg/dL)
      (a) If persistently elevated and ASCVD risk ≥7.5%, consider initiation or intensification of statin therapy
      (b) Reasonable to implement a very low-fat diet and reasonable to initiate fibrate or omega-3 fatty acid therapy to prevent acute pancreatitis, especially if fasting TG ≥ 1000 mg/dL
   v. Expected changes in TG concentrations with drug therapy (Table 16)

Table 16. Effect of Lipid-Lowering Medications on TG

Medication	% Decrease in TG
Statins	7–30
Fibrates	20–50
Ezetimibe	5–11
Omega-3 fatty acids	19–44

TG = triglycerides

E. Risk assessment tools for primary prevention
   1. Risk discussions and shared decision making with patients should consider whether lifestyle and ASCVD risk factors have been addressed, cost considerations, and a discussion of the potential benefits and adverse events of drug therapy. Patients and health care professionals should work together to establish a customized cholesterol management plan.
   2. Pooled Cohort Equation (PCE) to estimate 10-year ASCVD risk
      a. Measures hard ASCVD events: fatal and nonfatal MI and stroke
      b. Assists with identifying higher-risk patients for statin therapy
      c. Should not be used for patients with clinical ASCVD
      d. Available at http://tools.acc.org/ASCVD-Risk-Estimator/
      e. Components of PCE:
         i. Sex
         ii. Age
         iii. Race
         iv. TC
         v. HDL-C
         vi. SBP
         vii. Receiving treatment for high BP
         viii. Diabetes
         ix. Smoking status
   3. Risk-enhancing factors
      a. Family history of premature ASCVD (males <55 years, females <65 years)
      b. Primary hypercholesterolemia (LDL-C 160-189 mg/dL or non-HDL-C 190-219 mg/dL)
      c. Metabolic syndrome
      d. CKD
      e. Chronic inflammatory conditions such as psoriasis, rheumatoid arthritis, HIV/AIDS
      f. History of premature menopause (age <40 years)
      g. History of preeclampsia
      h. High-risk race/ethnicity (e.g., South Asian ancestry)
      i. Elevated TG ≥175 mg/dL
      j. Elevated biomarkers such as high-sensitivity C-reactive protein, lipoprotein (a), apolipoprotein B
      k. Ankle-brachial index <0.9
   4. Coronary artery calcium (CAC) score for additional risk-stratification
      a. If risk decision is uncertain (especially borderline and intermediate risk patients), consider measuring coronary artery calcium
      b. Score = 0: consider no statin (unless diabetes, family history of premature coronary artery disease, or cigarette smoking present)
      c. Score = 1-99: favors statin if age ≥55
      d. Score ≥100 *or* ≥75th percentile: favors statin

F. Monitoring
   1. Measure fasting lipids 4-12 weeks after therapy initiation
   2. Measure fasting lipids every 3-12 months thereafter
   3. Periodically re-assess risk factors for ASCVD

G. 3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins)
   1. General approach to initiating statin therapy:
      a. Fasting lipid panel
         i. If baseline LDL-C is higher than 190 mg/dL, evaluate for secondary causes. If primary, screen for familial hypercholesterolemia.

   b. Alanine aminotransferase (ALT)
      i. Evaluate patients with unexplained ALT more than 3x upper limit of normal
   c. Creatine kinase (if indicated)
   d. Evaluate for secondary causes or conditions that may affect statin safety
2. Efficacy
   a. First line for high LDL-C or ASCVD risk
   b. When selecting a statin, consider its intensity (Table 17).
   c. Reduce LDL-C by 24%–60%.
   d. Reduce TG by 7%–30%.
   e. Raise HDL-C by 5%–15%.
   f. Reduce major coronary events.
   g. Reduce CV mortality.
   h. Reduce coronary procedures (percutaneous coronary intervention [PCI] or coronary artery bypass grafting).
   i. Reduce stroke.
   j. Reduce total mortality.

Table 17. Relative LDL-C-Lowering Efficacy of Statins

Atorva (mg)	Fluva (mg)	Pitava (mg)	Lova (mg)	Prava (mg)	Rosuva (mg)	Simva (mg)	%↓ LDL
—	20–40	1	20	10–20	—	10	30
10	80	2	40	40	—	20	38
20	—	4	80	80	5	40	41
40	—	—	—	—	10	—	47
80	—	—	—	—	20	—	55
—	—	—	—	—	40	—	63

Denotes low-intensity statin; lowers LDL-C by < 30%.
Denotes moderate-intensity statin; lowers LDL-C by 30% to < 50%.
Denotes high-intensity statin; lowers LDL-C by ≥ 50%.

Atorva = atorvastatin; Fluva = fluvastatin; LDL-C = low-density lipoprotein cholesterol; Lova = lovastatin; Pitava = pitavastatin; Prava = pravastatin; Rosuva = rosuvastatin; Simva = simvastatin.

Adapted from: Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA guidelines on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults. Circulation 2014;129(suppl 2):S1-45.

3. Mechanism of action: Inhibits enzyme responsible for converting HMG-CoA to mevalonate (rate-limiting step in production of cholesterol)
4. Main adverse effects and monitoring
   a. Myopathy (can check creatine kinase [CK] at baseline and then only if muscle symptoms occur; no regular monitoring)
   b. Elevated liver enzymes
      i. Obtain LFTs at baseline in all patients
      ii. Perform repeated LFTs only when clinically indicated.
      iii. Monitor for symptoms of hepatic injury.
5. Absolute contraindications
   a. Active liver disease, unexplained persistent elevations in hepatic transaminases
   b. Breast/chestfeeding

c. Certain medications (agent-specific; see drug interactions below)
d. In 2021, the FDA requested removal of the contraindication against statin use in pregnancy. However, statins are teratogenic and should be discontinued in most patients who are pregnant or breast/chestfeeding.

6. Select drug interactions (see Table 18)
   a. Fibrates: Increased risk of myopathy and rhabdomyolysis when coadministered with statins. Risk is greater with gemfibrozil than with fenofibrate.
   b. Niacin: Doses greater than 1 g/day increase the risk of myopathy and rhabdomyolysis when used concomitantly with statins; risk is lower than with fibrates; statins and niacin are commonly used together; monitor for muscle pain.
   c. Canagliflozin: A case report of a myopathy attributed to a drug interaction between canagliflozin and rosuvastatin was recently reported.
7. Differences exist between statins in regard to pharmacokinetics and renal dosing (Tables 19 and 20)

Table 18. Select Drug Interactions with Statins

	Lovastatin	Pravastatin	Simvastatin	Fluvastatin	Pitavastatin	Atorvastatin	Rosuvastatin
Amiodarone	Daily dose NTE 40 mg		Daily dose NTE 20 mg				
Amlodipine			Daily dose NTE 20 mg				
Azole antifungals	CI (itraconazole, ketoconazole, posaconazole, and voriconazole)		CI (itraconazole, ketoconazole, posaconazole, and voriconazole)	Daily dose NTE 20 mg BID (fluconazole)		Daily dose NTE 20 mg (itraconazole)	
Bempedoic acid		Daily dose NTE 40 mg	Daily dose NTE 20 mg				
Cobicistat-containing products	CI		CI				
Colchicine	Use with caution	Use with caution	Use with caution	Use with caution	Use with caution	Use with caution	Use with caution
Cyclosporine	Avoid use	Daily dose NTE 20 mg	CI	Daily dose NTE 20 mg BID	CI	Avoid use	Daily dose NTE 5 mg
Danazol	Daily dose NTE 20 mg		CI				
Diltiazem Verapamil	Daily dose NTE 20 mg		Daily dose NTE 10 mg				
Dronedarone	Daily dose NTE 20 mg		Daily dose NTE 10 mg				
Erythromycin Clarithromycin	CI	Daily dose NTE 40 mg (clarithromycin)	CI		Daily dose NTE 1 mg (erythromycin)	Daily dose NTE 20 mg (clarithromycin)	
Gemfibrozil	Avoid use	Avoid use	CI	Avoid use	Avoid use	Avoid use	Daily dose NTE 10 mg
Grapefruit juice (> 1 quart per day)	Avoid use		Avoid use			Avoid excess quantities (> 1.2 L/day)	
Lomitapide	Consider lovastatin dose reduction		Daily dose NTE 20 mg (or 40 mg if tolerated 80 mg for ≥1 yr)				
Nefazodone	CI		CI				
Niacin	Avoid doses of niacin ≥ 1 g/day	Avoid doses of niacin ≥ 1 g/day	Avoid doses of niacin ≥ 1 g/day	Avoid doses of niacin ≥ 1 g/day	Avoid doses of niacin ≥ 1 g/day	Avoid doses of niacin ≥ 1 g/day	Use with caution

Table 18. Select Drug Interactions with Statins (*Cont'd*)

	Lovastatin	Pravastatin	Simvastatin	Fluvastatin	Pitavastatin	Atorvastatin	Rosuvastatin
HIV protease inhibitors	CI		CI			Avoid use with tipranavir plus ritonavir. Daily dose NTE 20 mg (saquinavir/ritonavir, darunavir/ritonavir, fosamprenavir or fosamprenavir/ritonavir) Daily dose NTE 40 mg (nelfinavir)	Daily dose NTE 10 mg (lopinavir/ritonavir or atazanavir/ritonavir)
Ranolazine	Consider dose adjustment		Daily dose NTE 20 mg				
Rifampin					Daily dose NTE 2 mg		

BID = twice daily;

CI = contraindicated; HIV = human immunodeficiency virus; NTE = not to exceed.

Table 19. Pharmacokinetic Differences Between Statins

	Bioavailability (%)	Half-life (hr)	Elimination/ Metabolism	Prodrug	Solubility
Atorvastatin	14	14	3A4	No	Lipophilic
Fluvastatin	24	3	2C9	No	Lipophilic
Lovastatin	< 5	2–3	3A4	Yes	Lipophilic
Pitavastatin	43-51	12	2C9	No	Lipophilic
Pravastatin	17	1.8	N/A	No	Hydrophilic
Simvastatin	< 5	2	3A4	Yes	Lipophilic
Rosuvastatin	20	19	2C9	No	Hydrophilic

N/A = not applicable.

Table 20. Dosing of Statin Agents in CKD

Drug	Comments	Dose Recommended by KDIGO Guidelines[a]
Atorvastatin	—	20 mg/day
Fluvastatin	Doses > 40 mg/day not studied in severe renal impairment	80 mg/day
Lovastatin	CrCl <30 mL/min: NTE 20 mg/day	Not studied
Pitavastatin	CrCl 15-59 mL/min: NTE 2 mg/day	2 mg/day
Pravastatin	CrCl <30 mL/min: Initial dose = 10 mg/day	40 mg/day
Simvastatin[b]	CrCl < 30 mL/min: Initial dose = 5 mg/day	40 mg/day (ezetimibe/simvastatin 10/20 mg/day)
Rosuvastatin	CrCl < 30 mL/min: NTE 10 mg/day	10 mg/day

[a]Recommendations for Stage 3a through Stage 5 CKD (from Kidney Disease: Improving Global Outcomes Lipid Work Group. KDIGO clinical practice guidelines for lipid management in chronic kidney disease. Kidney Int 2013;3:1-56).

[b]The 80-mg dose of simvastatin should be reserved for patients who have been taking simvastatin 80 mg long term (e.g., ≥ 12 mo) and who are without evidence of muscle toxicity.

CrCl = creatinine clearance; NTE = not to exceed

H. Ezetimibe
   1. Efficacy
      a. Lowers LDL-C by 18%–20%
      b. Can raise HDL-C by 1%–5%
      c. Lowers TG by 5%–10%
   2. Mechanism of action: Inhibition of cholesterol absorption
   3. Adverse effects and monitoring: Diarrhea, upper respiratory tract symptoms; no monitoring necessary
   4. Data suggest that combination with simvastatin is superior to simvastatin alone in prevention of CV events.

I. PCSK9 Inhibitors
   1. Monoclonal antibodies (mAbs)
      a. Agents: Alirocumab, evolocumab
      b. Efficacy: Lower LDL-C by an additional 45%–68% when combined with statin therapy; reduce CV events when added to statin therapy (FOURIER and ODYSSEY OUTCOMES trials)
      c. Mechanism of action: Monoclonal antibodies that inhibit a protein called PCSK9, increasing cholesterol clearance from the liver
      d. Both indicated for heterozygous familial hypercholesterolemia or clinical ASCVD; evolocumab also indicated for homozygous familial hypercholesterolemia
      e. According to the 2018 AHA/ACC management of blood cholesterol guidelines, PCSK9 mAbs are only indicated for select patients already receiving maximally tolerated statin therapy and ezetimibe with either clinical ASCVD at very high risk or severe hypercholesterolemia in the 2018 ACC/AHA cholesterol guidelines (Figure 7). According to the 2022 ACC expert consensus pathway on nonstatin therapy, either PCSK9 mAbs or ezetimibe may be considered as first-line adjuvants to maximally tolerated statin therapy.
      f. Adverse effects: Injection-site reactions, respiratory infections
      g. Dose:
         i. Evolocumab:
            (a) Heterozygous familial hypercholesterolemia or clinical ASCVD: 140 mg subcutaneously every 2 weeks or 420 mg subcutaneously once monthly
            (b) Homozygous familial hypercholesterolemia: 420 mg subcutaneously once monthly
         ii. Alirocumab: Initial dose, 75 mg subcutaneously every 2 weeks or 300 mg subcutaneously every 4 weeks; if LDL-C reduction inadequate, can adjust dose to 150 mg subcutaneously every 2 weeks
         iii. PCSK9 inhibitor mAbs are preferred to inclisiran because of availability of CV outcomes data.
   2. Inclisiran
      a. Efficacy: Reduces LDL by 51%
      b. Mechanism of action: Small synthetic interfering ribonucleic acid that inhibits translation of PCSK9 proteins, up-regulating hepatic LDL receptor density
      c. Indicated as an adjunct to maximally tolerated statin therapy in adults with heterozygous familial hypercholesterolemia or ASCVD who require additional LDL lowering
      d. Adverse effects: Injection site reactions
      e. Dose: 284 mg subcutaneously at months 0 and 3, then every 6 months thereafter
      f. Clinical outcomes trials are ongoing. To date, the effect of inclisiran on CV morbidity and mortality is unknown.

J. Bile acid sequestrants (cholestyramine, colestipol, colesevelam)
   1. Efficacy
      a. Reduce LDL-C by 15%–27%.
      b. Raise HDL-C by 3%–5%.
      c. May increase TG concentrations.
      d. Reduce major coronary events.

2. Mechanism of action: Bind to bile acids to disrupt enterohepatic recirculation of bile acids. Liver is stimulated to convert hepatocellular cholesterol to bile acids.
3. Adverse effects: GI distress, constipation
4. Decreased absorption of many drugs including: warfarin, amiodarone, levothyroxine, ezetimibe, digoxin, and thiazides; administer drugs 1–2 hours before or 4 hours after bile acid sequestrant
5. Contraindications: Complete biliary obstruction, raised TG concentrations (especially greater than 400 mg/dL)

K. Fibrates (gemfibrozil, fenofibrate, fenofibric acid)
1. Efficacy
   a. Lower LDL-C by 5%–20% (with normal TG)
   b. May raise LDL-C with very high TG
   c. Lower TG by 20%–50%
   d. Raise HDL-C by 10%–20%
2. Mechanism of action: Reduces rate of lipogenesis in the liver
3. Adverse effects and monitoring: Dyspepsia, gallstones, myopathy, increased hepatic transaminases. Monitor LFTs every 3 months during first year and then periodically.
4. Contraindications: Severe renal or hepatic disease, pre-existing gallbladder disease
5. Indicated for the treatment of severe hypertriglyceridemia (TGs 500 mg/dL or greater), especially in patients with TGs 1000 mg/dL or greater

L. Omega-3 fatty acids
1. Contain varying ratios of EPA and DHA
   a. Omega-3 acid ethyl esters: DHA and EPA
   b. Icosapent ethyl: EPA only
   c. Omega-3 carboxylic acid: DHA and EPA
2. Efficacy
   a. Lowers TG by 26%–45%
   b. Can raise LDL-C when TG concentrations are high
   c. Raises HDL-C by 5%–14%
   d. Icosapent ethyl reduced the composite of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina in the REDUCE-IT trial.
3. Mechanism of action: Reduction of hepatic production of very-low-density lipoproteins; possible reduction in hepatic synthesis of TG; increased hepatic β-oxidation
4. Adverse effects: Arthralgia, GI effects (e.g., burping, taste perversion, dyspepsia); at more than 3 g/day, bleeding (because of inhibition of platelet aggregation)
5. Dose: 2–4.8 g/day as a single dose or in two divided doses
6. Icosapent ethyl is FDA approved for CV event risk reduction among patients receiving statins and TG of 150 mg/dL or greater with either established ASCVD or diabetes plus additional CV risk factors .

M. Bempedoic Acid
1. Efficacy
   a. Lowers LDL-C by 15%–25%
   b. Reduces HDL-C by 5%
2. Mechanism of action: Inhibits ATP-citrate lyase, which inhibits cholesterol synthesis in the liver
3. Adverse effects and monitoring: Gout, hyperuricemia, leukopenia, thrombocytopenia, tendon rupture. Monitor for signs/symptoms of hyperuricemia and tendon rupture.
4. Indicated for use as an adjunct to statin therapy in heterozygous familial hypercholesterolemia or known CVD in patients who require additional LDL-C reduction

5. Also available as combination product with ezetimibe
6. In the recent CLEAR Outcomes trial, bempedoic acid was associated with reduced rates of major adverse cardiovascular events (MACE) compared with placebo among primary prevention patients with statin intolerance (N Engl J Med 2023;388:1353-64).
7. Bempedoic acid may be considered among patients who require modest LDL-C reductions with intolerance of other therapies or for ease of use among individuals who wish to avoid injectable therapies.

Patient Cases

8. M.M. is a 63-year-old woman who just finished 6 months of diet and exercise for dyslipidemia. She has a history of hypertension, diabetes, and asthma. She smokes one pack of cigarettes and drinks three beers per day. Her mother had HTN and suffered an MI at age 42 years. Her father had HTN and diabetes. Her medications are albuterol metered dose inhaler, lisinopril, metformin, linagliptin, and calcium carbonate antacids. Her vital signs include BP 134/84 mm Hg and HR 75 beats/minute. Her laboratory results are as follows: HDL-C 38 mg/dL, LDL-C 134 mg/dL, TG 186 mg/dL, TC 209 mg/dL, and hemoglobin A1C 8.6%. Her pooled cohort equation estimates a 10-year ASCVD risk of 27.8%. What is the most appropriate next step for M.M.?
   A. Initiate a low-intensity statin
   B. Initiate a moderate-intensity statin
   C. Initiate a high-intensity statin
   D. Initiate a high-intensity statin plus ezetimibe

9. According to the ACC/AHA blood cholesterol guidelines, which is best described as a high-intensity statin dose?
   A. Pravastatin 20 mg/day.
   B. Lovastatin 20 mg/day.
   C. Atorvastatin 40 mg/day.
   D. Rosuvastatin 10 mg/day.

10. Which best describes a potential secondary cause of high TG concentrations?
    A. Amiodarone.
    B. Biliary obstruction.
    C. Sirolimus.
    D. Saturated fats.

V. CHRONIC CORONARY DISEASE

A. Background
   1. Definition: CCD refers to patients who meet any of the following criteria:
      a. Stable outpatient with a history of acute coronary syndrome (ACS) or coronary revascularization
      b. Left ventricular systolic dysfunction or cardiomyopathy deemed the result of coronary disease
      c. Stable angina
      d. Vasospastic or microvascular angina
      e. Diagnosis on the basis of screening studies (e.g., stress test, CT angiography)
   2. Prevalence
      a. Diagnosed in 20.1 million persons living in the United States
      b. Around 11.1 million persons live with CCD.
      c. About 25% of MIs occur in patients with a history of MI.
      d. Remains the leading cause of death in the United States

3. A new guideline for management of CCD was published in 2023.
4. Patients with ACS (i.e., ST-segment elevation MI [STEMI], non–ST-segment elevation MI [NSTEMI], or unstable angina) are discussed in the Acute Care in Cardiology section.

B. Therapeutic Management Overview
   1. Guiding principles: The 2023 AHA/ACC guidelines emphasize:
      a. Prioritizing therapies according to the risk of CVD-related events
      b. First steps may prioritize symptom relief, and quality of life may be appropriate as a component of shared decision-making.
      c. Social determinants of health such as health care access, economic stability, and social context should be considered in care plans.
      d. Care should be interprofessional and collaborative.
   2. Goals of therapy
      a. Prolong survival
      b. Improve quality of life

C. Diet and Lifestyle
   1. Physical activity: In the absence of contraindications, encourage:
      a. At least 150 minutes/week of moderate-intensity aerobic activities *or* at least 75 minutes/week of high-intensity aerobic activities
      b. Resistance training at least 2 days/week
      c. Encourage any activities that may reduce sedentary behaviors (e.g., taking the stairs, gardening).
   2. Nutrition
      a. Emphasize a diet rich in fruits, vegetables, nuts, whole grains, and lean proteins.
      b. Avoid *trans* fats.
      c. Saturated fats should comprise less than 6% of total calories.
      d. Sodium restriction to less than 2300 mg/day (less than 1500 mg/day is optimal)
      e. Limit refined carbohydrates (e.g., cereals, white rice) and sugar-added drinks.
      f. Non-prescription dietary supplements such as omega-3 fatty acids, vitamins, and calcium are not beneficial in reducing the risk of CVD events.
   3. Environmental exposures
      a. Minimize exposure to ambient air pollution.
      b. Minimize climate-related exposures (e.g., extreme temperatures, wildfire smoke).

D. Antithrombotic Therapy
   1. Antithrombotic therapy is recommended in patients with CCD to reduce the risk of ASCVD events.
   2. Selection of antithrombotic agents depends on the patient's prior ASCVD events, history of PCI with drug-eluting stent (DES), bleeding risk, and comorbidities.
   3. Antithrombotic recommendations for individuals who do not have a primary indication for anticoagulation are located in Figure 8.
      a. Low-dose aspirin (75–100 mg) is the recommended dose in CCD.
      b. Single antiplatelet therapy (SAPT) indicates use of either low-dose aspirin or a $P2Y_{12}$ inhibitor. Results of the PANTHER study indicated that long-term $P2Y_{12}$ inhibitor monotherapy is associated with a reduction in MACE and bleeding rates similar to aspirin monotherapy (J Am Coll Cardiol 2023;82:89-105).
      c. Individuals undergoing PCI without a history of ACS being treated with dual antiplatelet therapy (DAPT) should receive clopidogrel plus aspirin.
      d. Individuals with a history of ACS treated with PCI may receive clopidogrel, ticagrelor, or prasugrel as a component of DAPT.

e. Reasonable to extend DAPT beyond 12 months and up to 3 years to reduce MACE in individuals who have had a previous MI and are at a low bleeding risk
f. Addition of clopidogrel to aspirin is not recommended to reduce MACE in individuals with CCD without a recent ACS or PCI.

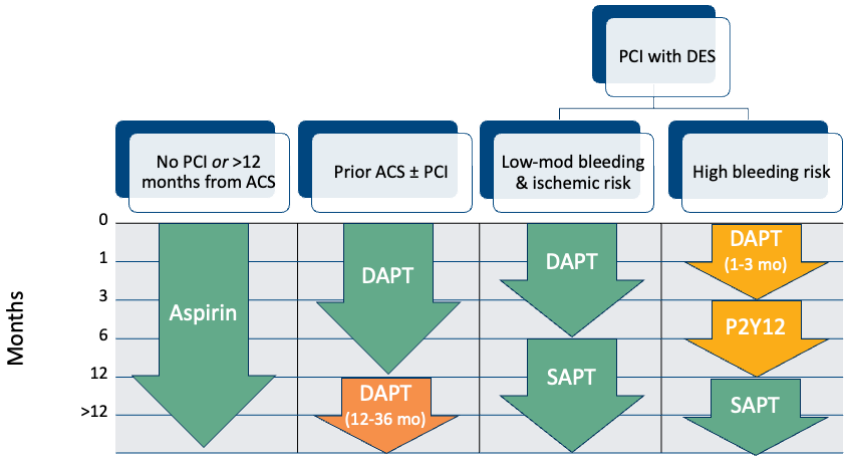


Figure 8. Antiplatelet therapy recommendations for patients with chronic coronary disease.

ACS = acute coronary syndrome; DAPT = dual antiplatelet therapy; DES = drug-eluting stent; mod = moderate; $P2Y_{12}$ = $P2Y_{12}$ receptor antagonist; PCI = percutaneous coronary intervention; SAPT = single antiplatelet therapy.

Information from: Virani SS, Newby LK, Arnold SV, et al. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA guideline for the management of patients with chronic coronary disease. J Am Coll Cardiol 2023;82:833-955.

4. Antithrombotic recommendations for individuals on chronic anticoagulation are located in Figure 9.
   a. Patients receiving triple antithrombotic therapy should receive a DOAC plus clopidogrel plus low-dose aspirin (75–100 mg).
5. In patients who have no indication for therapeutic anticoagulation or DAPT but who are at high risk of recurrent ASCVD events and low to moderate bleeding risk, it is reasonable to add rivaroxaban 2.5 mg twice daily to low-dose aspirin to reduce the risk of MACE.

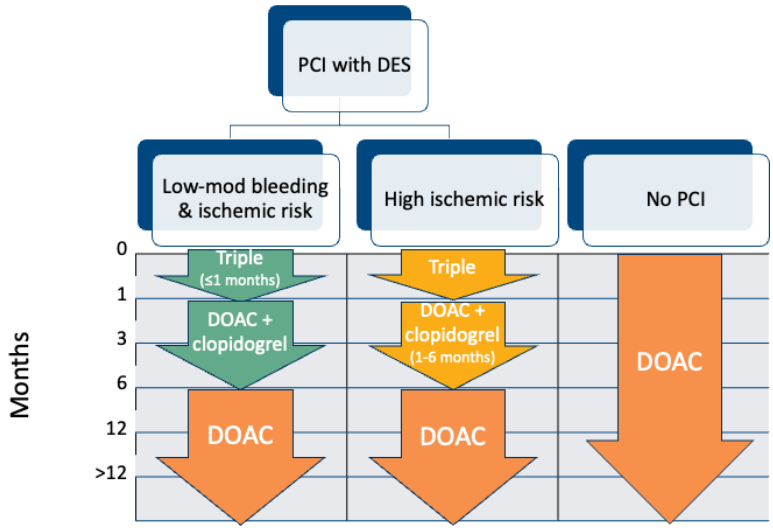


Figure 9. Antithrombotic recommendations for patients with chronic coronary disease and a primary indication for anticoagulation.

DES = drug-eluting stent; DOAC = direct-acting oral anticoagulant; mod = moderate; PCI = percutaneous coronary intervention.

Information from: Virani SS, Newby LK, Arnold SV, et al. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA guideline for the management of patients with chronic coronary disease. J Am Coll Cardiol 2023;82:833-955.

Patient Case

11. A 66-year-old man with a medical history of HTN and ACS with a drug-eluting coronary stent placement 14 months ago presents to the primary care clinic. Current medications include aspirin 81 mg/day, prasugrel 10 mg/day, nitroglycerin 0.4-mg sublingual tablets as needed for chest pain, metoprolol succinate 75 mg/day, ramipril 10 mg/day, and atorvastatin 20 mg/day. He asks you how long he will need to take prasugrel. What is the best answer?

    A. Call your physician because you may be able to stop prasugrel now.

    B. Your prasugrel should have been discontinued 6 months after ACS; discontinue it now.

    C. You will need to take prasugrel indefinitely.

    D. You will need to take prasugrel for at least 18 months after your MI and stent placement.

E. Management of Chronic Coronary Disease

1. Goals: Reduce symptoms of ischemia, increase physical function, and improve quality of life. In general, achieved by either decreasing myocardial oxygen demand or increasing myocardial oxygen supply
2. Management algorithm (Figure 10)
    a. First-line therapies for relief of anginal symptoms include ß-blockers, CCBs, or long-acting nitrates.
    b. If relief is inadequate, a second agent from a different class may be added.
    c. Ranolazine is an appropriate third-line agent for relief of angina.
    d. In addition, all patients should have a prescription for sublingual or nasal nitroglycerin.

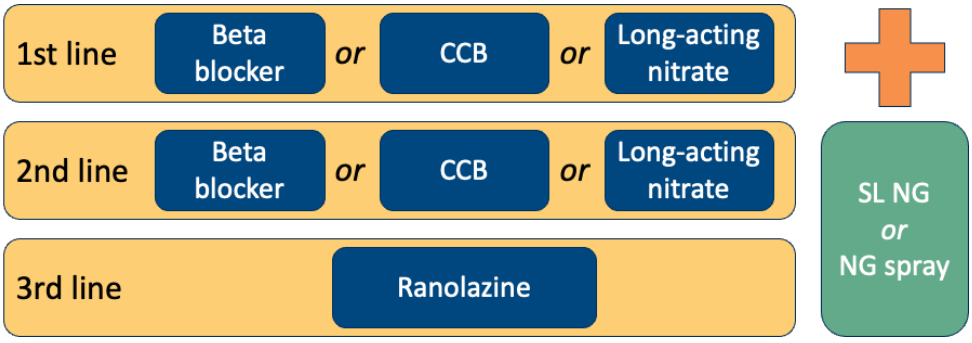


Figure 10. Management of anginal symptoms.

CCB = calcium channel blocker; NG = nitroglycerin; SL = sublingual.

Information from: Virani SS, Newby LK, Arnold SV, et al. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA guideline for the management of patients with chronic coronary disease. J Am Coll Cardiol 2023;82:833-955.

4. Specific agents
    a. β-Blockers
        i. Pharmacologic effects: Decreased inotropy and HR (decrease oxygen demand)
        ii. Place in therapy: May be considered a first- or second-line chronic therapy for all patients with CCD and stable angina. Prioritize ß-blockade in the first year after an MI.
        iii. Contraindications: Severe bradycardia (HR less than 50 beats/minute), high-degree AV block or sick sinus syndrome (in absence of a pacemaker)
    b. CCBs
        i. Pharmacologic effects
            (a) Decrease coronary vascular resistance and increase coronary blood flow (increase oxygen supply)

(b) Negative inotropy, to varying degrees; nifedipine much greater than amlodipine and felodipine (decrease oxygen demand)
(c) Decrease HR (verapamil and diltiazem only; decrease oxygen demand)

ii. Place in therapy
(a) CCBs may be considered a first- or second-line chronic therapy for all patients with CCD and stable angina.
(b) Non-DHP CCBs should be used with caution in addition to ß-blocker therapy because of the risk of additive bradycardia or heart block.

iii. Short-acting CCBs (nifedipine) have been associated with increased CV events; should be avoided (except in slow-release formulations)

iv. Contraindications for non-DHP CCBs: HFrEF, severe bradycardia, high-degree AV block or sick sinus syndrome (in absence of a pacemaker)

c. Nitrates
i. Pharmacologic effects:
(a) Endothelium-dependent vasodilation, dilates epicardial arteries and collateral vessels (increase oxygen supply)
(b) Decreased left ventricular volume because of decreased preload mediated by venodilation (decrease oxygen demand)

ii. Place in therapy
(a) Scheduled long-acting nitrates may be considered a first- or second-line chronic therapy for all patients with CCD and stable angina.
(b) As-needed sublingual tablets, powder, or spray nitroglycerin is necessary to relieve effort or rest angina.
(c) In addition, as-needed sublingual or spray nitroglycerin can be used before exercise to avoid ischemic episodes. Nitroglycerin spray has shown greater efficacy and efficiency at relieving anginal symptoms than sublingual nitroglycerin and results in fewer headaches.

iii. Caution: Hypertrophic obstructive cardiomyopathy, inferior wall MI, severe aortic valve stenosis, avanafil within 12 hours, sildenafil and vardenafil within 24 hours, tadalafil within 48 hours

d. Ranolazine
i. Pharmacologic effects
(a) Inhibits the late phase of the inward Na channel in ischemic myocytes during repolarization, leading to a reduction in intracellular Na concentrations. This reduction in Na concentrations leads to reduced calcium influx, which decreases ventricular tension and myocardial oxygen consumption.
(b) Increases "oxygen efficiency"

ii. Place in therapy
(a) May be considered as a third-line therapy for patients with CCD and stable angina in combination with β-blockers, CCBs, and/or nitrates when initial management with these drugs is unsuccessful
(b) Can also consider as alternative therapy when blood pressure or heart rate is too low to add β-blockers, CCBs, and/or nitrates
(c) Also causes modest reduction in A1C
(d) Important points
(1) No significant effects on HR or BP; thus, bradycardia and hypotension are not of concern
(2) Dose-related QT interval prolongation
(3) Metabolized by CYP3A; P-gp substrate
(A) Avoid in hepatic dysfunction.

(B) Avoid use with strong CYP3A inhibitors, including ketoconazole, itraconazole, clarithromycin, nefazodone, nelfinavir, ritonavir, indinavir, and saquinavir.
(C) Avoid use with CYP3A inducers such as rifampin, rifabutin, rifapentine, phenobarbital, phenytoin, carbamazepine, or St. John's wort.
(D) Limit the dose to 500 mg twice daily in patients receiving moderate CYP3A4 inhibitors, including diltiazem, verapamil, erythromycin, fluconazole, and grapefruit juice.

F. Blood Pressure Management and Antihypertensives
1. Treatment algorithm (Figure 11)
a. Blood pressure should be maintained at less than 130/80 mm Hg.
b. First-line pharmacotherapy includes ACE inhibitor/ARBs or ß-blockers in patients with a history of recent MI or angina.
c. Additional antihypertensive medications (e.g., DHP CCBs, thiazide diuretics, and MRAs) should be added as needed to optimize blood pressure control.

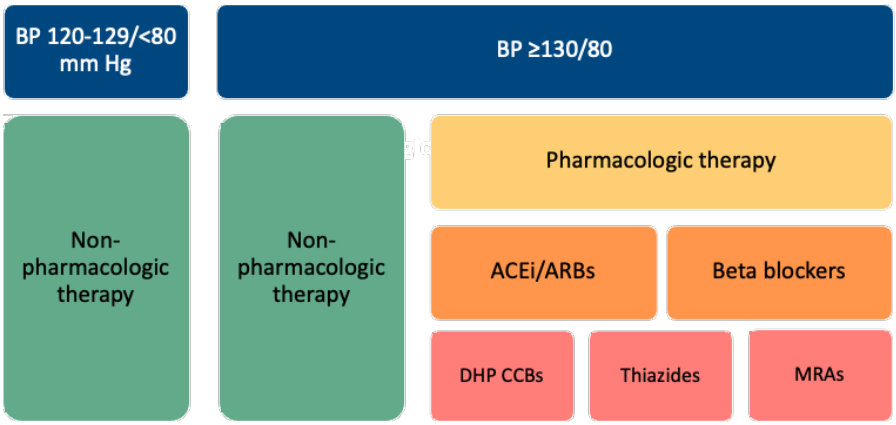


Figure 11. Blood pressure management and antihypertensive therapy in chronic coronary disease.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BP = blood pressure; CCB = calcium channel blocker; DHP = dihydropyridine; MRA = mineralocorticoid receptor antagonist.

Information from: Virani SS, Newby LK, Arnold SV, et al. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA guideline for the management of patients with chronic coronary disease. J Am Coll Cardiol 2023;82:833-955.

d. ß-Blockers
i. Compelling indications to prioritize ß-blockers include LVEF of 40% or less with or without previous MI.
ii. In patients with CCD and an LVEF of 50% or less receiving ß-blockers, preference should be given to metoprolol succinate, carvedilol, or bisoprolol titrated to target dose over other agents.
iii. It is reasonable to reassess the need for ß-blockers after 1 year in patients with a previous MI who do not have an LVEF of 50% or less, angina, arrhythmias, or uncontrolled HTN.
iv. ß-Blockers are not beneficial in reducing MACE in patients without a history of MI, LVEF of 50% or less, or another primary indication.
e. ACE inhibitors and ARBs
i. Compelling indications to prioritize ACE inhibitors (or ARBs if ACE inhibitors are not tolerated) for the prevention of CV events include HTN, diabetes, HFrEF, and CKD.
ii. ACE inhibitors or ARBs may be considered to reduce CV events in the absence of other primary indications.

G. Lipid Management
   1. All patients with CCD should receive a high-intensity statin with a goal of 50% or greater LDL-C reduction.
   2. Patients who cannot tolerate high-intensity statin therapy may receive moderate-intensity statins with a goal of 30%–49% LDL-C reduction.
   3. Risk of future ASCVD events and LDL-C concentrations guide selection of additional lipid-lowering therapy (Figure 12).
   4. Risk assessment
      a. Patients are deemed at very high risk if they have a history of multiple major ASCVD events *or* one major ASCVD event and at least two high-risk conditions.
      b. Major ASCVD events include ACS in the past 12 months, history of MI other than recent ACS, history of ischemic stroke, or symptomatic PAD (i.e., claudication with ankle-brachial index less than 0.85 or previous revascularization or amputation).
      c. High-risk conditions include age older than 65 years, familial hypercholesterolemia, history of coronary artery bypass grafting or PCI outside of major ASCVD events, persistent LDL-C 100 mg/dL or greater despite statin and ezetimibe therapy, diabetes, HTN, CKD (eGFR 15–59 mL/min/1.73 m^2), congestive heart failure, and current tobacco smoking.

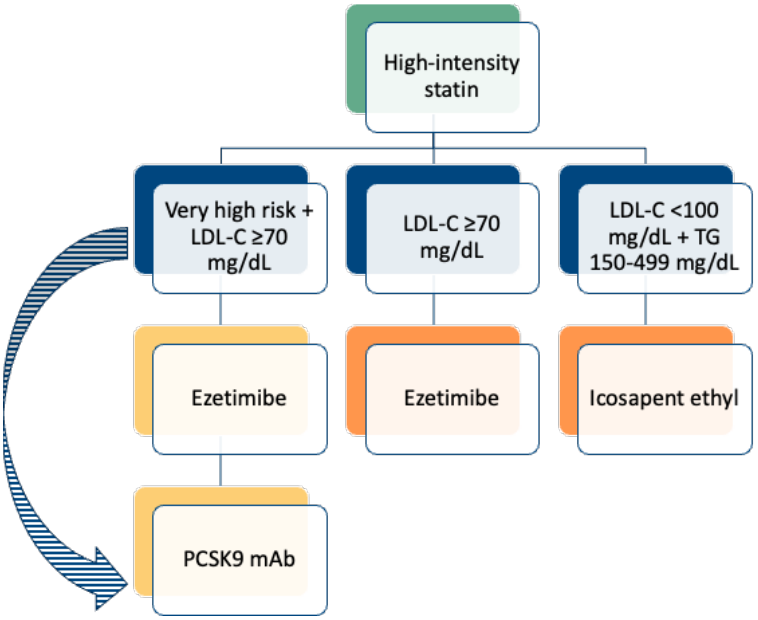


Figure 12. Lipid therapy in patients with chronic coronary disease.
PCSK9 = proprotein convertase subtilisin/kexin type 9 serine protease.

   5. Patients with an LDL-C of 70 mg/dL or greater who are deemed at very high risk may alternatively receive PCSK9 mAb therapy in place of ezetimibe therapy, but ezetimibe has a high cost value, and the value of PCSK9 mAbs is considered uncertain.
   6. In patients with an LDL-C of 70 mg/dL or greater in whom ezetimibe or PCSK9 mAbs are deemed insufficient or not tolerated, it may be reasonable to add bempedoic acid or inclisiran (instead of PCSK9 mAbs) to further reduce LDL-C.
   7. In patients treated with statins, the use of niacin, fenofibrate, or dietary supplements containing omega-3 fatty acids is not beneficial to reduce CV risk.
   8. See Dyslipidemia section for additional information about each drug/drug class.

H. SGLT2i and Glucagon-Like Peptide 1 Receptor Antagonists (GLP-1RAs)
   1. SGLT2i and GLP-1RA therapy is recommended in several subsets of patients with CCD to further reduce CV risk (Table 21).

Table 21. Role of Sodium-Glucose Cotransporter 2 Inhibitor and Glucagon-Like Peptide 1 Receptor Antagonist Therapies in Chronic Coronary Disease

	Glucagon-like Peptide 1 Receptor Antagonists	**Sodium-Glucose Cotransporter 2 Inhibitors**
Diabetes	Recommended to reduce MACE	Recommended to reduce MACE
HFrEF		Recommended to reduce CV death and HF hospitalizations and improve quality of life
HF (LVEF > 40%)		May be beneficial to reduce HF hospitalizations and improve quality of life
Overweight/obesity	In addition to diet and lifestyle when pharmacologic therapy is warranted for further weight reduction (semaglutide > liraglutide)	

CV = cardiovascular; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; MACE = major adverse cardiovascular events.

I. Adjunctive Therapies
   1. Individuals with CCD should remain up-to-date on recommended vaccinations, including pneumococcal, annual influenza, and recommended COVID-19 vaccinations.
   2. Colchicine may be considered for secondary prevention to reduce recurrent ASCVD events.
   3. Smoking cessation should be encouraged.
   4. Limiting or avoiding alcohol and substance use is recommended.
   5. Individuals should be screened and treated for mental health conditions.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: C

This patient has NYHA class III HFrEF with an LVEF of 20%. The best option is to add empagliflozin 10 mg orally daily to reduce CV mortality and HF hospitalizations (Answer C is correct). Appropriate monitoring would include signs and symptoms of hypotension and genitourinary infections. Although increasing this patient's carvedilol dose (Answer A) is desirable long term, the patient currently has signs and symptoms of fluid overload; adding or increasing doses of ß-blockers is not advisable in this setting. The ACE inhibitor is already at the maximum recommended lisinopril dose for HF; therefore, further increases are not warranted (Answer B). Her digoxin concentration of 0.7 ng/dL is within the desired range of 0.5–0.9 ng/mL; therefore, no dose increase is warranted because this would not improve efficacy and would only increase the risk of toxicity (Answer D).

2. Answer: B

An ACE inhibitor or ARB should be changed to an ARNI in all patients with HFrEF, if possible (Answer B is correct). This patient's blood pressure and SCr safely permit this change. Because the patient was taking a low dose of enalapril, the appropriate starting dose for sacubitril/valsartan is 24/26 mg orally twice daily. The clinician should remember to allow a 36-hour washout period between ACE inhibitor and ARNI doses. There is no consensus that carvedilol is preferred to extended-release metoprolol for patients with HFrEF (Answer A is incorrect). Spironolactone is not appropriate to initiate in this patient because his baseline SCr concentration is greater than 2.5 mg/dL (Answer C is incorrect). Digoxin should be added only in patients who continue to have symptoms or hospitalizations despite optimized therapy with an ACE inhibitor/ARB/ARNI, β-blocker, MRA, SGLT2 inhibitor, and diuretic, and this patient's therapy is not considered optimal. In addition, digoxin 0.125 mg daily would likely be too high for a patient with an SCr of 2.8 mg/dL. This patient's ACE inhibitor therapy is not considered optimal (Answer D is incorrect).

3. Answer: C

Cilostazol, a phosphodiesterase type 3 inhibitor, may be associated with an elevated risk of ventricular arrhythmias and death in patients with HFrEF (Answer C). Acetaminophen is the drug of choice for mild to moderate pain in patients with HF, because NSAIDs can lead to water retention and worsening HF symptoms (Answer A). The selective serotonin reuptake inhibitors are not contraindicated in HF (Answer B). Properly dosed thyroid replacement therapy, as evidenced by his therapeutic thyroid-stimulating hormone concentration, is also beneficial because both hypothyroidism and hyperthyroidism have negative consequences in patients with HF (Answer D).

4. Answer: D

This patient's ventricular rate is well controlled with his metoprolol tartrate therapy; therefore, an additional AV nodal-blocking agent is unnecessary and would increase the risk of adverse events and heart block. If additional rate control is desired, the metoprolol dose could first be increased, but the patient's heart rate is currently within the goal range (Answers A and B are incorrect). This patient with AF would be considered at high risk of a stroke because of his history of HTN and TIA. Given these risk factors, this patient has a CHA_2DS_2-VASc score of 3; therefore, anticoagulation with an oral anticoagulant agent is indicated. Warfarin titrated to a goal INR of 2.5 would be a potentially appropriate option; however, this patient may be unable to travel to his primary care provider's office for weekly INR checks, and DOACs are preferred to warfarin for DOAC-eligible patients (Answer C). In this case, dabigatran 150 mg twice daily (Answer D) may be the best choice because it does not warrant INR monitoring, the patient has prescription insurance, he appears to be adherent to a twice-daily medication regimen already, and he does not have renal impairment.

5. Answer: C

With the new diagnosis of HFrEF, this patient can no longer receive sotalol. Discontinuing this medication is important so that his risk of arrhythmic death is not increased. Adding metoprolol is a reasonable approach, but not until his HF has been properly controlled, making both Answers A and D incorrect. If rhythm control is desired, amiodarone and dofetilide are the only two antiarrhythmic drugs that have been proven safe and effective in patients with HFrEF, making Answer C correct. Of importance, drug interactions exist between amiodarone, digoxin, and warfarin, which will need to be addressed. Dronedarone (Answer B) is not

recommended in patients with symptomatic HF with a recent decompensation.

6. Answer: B
W.D.'s blood pressure falls into the stage 2 HTN category. The ACC/AHA guidelines recommend two-drug therapy for patients with stage 2 HTN, making answers A and D incorrect. This patient recently suffered from a myocardial infarction, and the ACC/AHA guidelines recommend both β-blockers and ACE inhibitors or ARBs for treatment of HTN in ischemic heart disease, making answer B correct and Answer C incorrect.

7. Answer: B
T.J.'s blood pressure falls into the stage 1 HTN category. Because the patient's 10-year ASCVD risk is 10% or greater, her blood pressure treatment threshold is 130/80 mm Hg or greater. Therefore, pharmacologic treatment is warranted, making Answer A incorrect. Because she has stage 1 HTN, she should be started on a single drug regimen, making answer D incorrect. According to the ACC/AHA guidelines, patients without medical conditions that direct drug therapy choices can be initiated on ACE inhibitors, ARBs, thiazide diuretics, or calcium channel blockers. However, because this patient is African American and she does not have heart failure, CKD, or type 2 diabetes with albuminuria, her initial HTN regimen should include a calcium channel blocker or a thiazide diuretic because these agents are more effective at lowering BP than ACE inhibitors and ARBs. Therefore, answer C is incorrect and answer B is the best choice.

8. Answer: C
This patient falls into the patient management group of patients with diabetes and age 40-75 years. Because she has multiple ASCVD risk factors including smoking, low HDL-C, and HTN, this patient would benefit from high-intensity statin therapy (answer C). Answer B would be correct if M.M. did not have additional ASCVD risk factors. Low-intensity statins are not recommended for initial therapy for any patient in the 2018 ACC/AHA Cholesterol guidelines (answer A). This patient should receive maximally tolerated statin therapy and be assessed for response before the addition of ezetimibe (Answer D).

9. Answer: C
A high-intensity statin should provide a ≥50% reduction in LDL-C. Atorvastatin 40 mg is considered a high-intensity statin because it will lower LDL by more than 50% (Answer C is correct). Pravastatin 20 mg (Answer A) and lovastatin 20 mg (Answer B) are considered low-intensity statins because they will lower LDL by less than 30%. Rosuvastatin 10 mg will reduce LDL 30%–50%; therefore, it is considered a moderate-intensity statin (Answer D).

10. Answer: C
If fasting TG concentrations are 500 mg/dL or greater or LDL-C is greater than 190 mg/dL, patients should be assessed for potential secondary causes of their dyslipidemia. Secondary causes of elevated TG include high intake of carbohydrates, excessive alcohol intake, oral estrogens, glucocorticoids, protease inhibitors, sirolimus (Answer C), thiazides, anabolic steroids, raloxifene, β-blockers, nephrotic syndrome, CKD, lipodystrophies, poorly controlled diabetes, hypothyroidism, pregnancy, and obesity. Amiodarone (Answer A), biliary obstruction (Answer B), and saturated fats (Answer D) are all secondary causes of increased LDL-C.

11. Answer: A
After placement of a DES for ACS, a $P2Y_{12}$ inhibitor is indicated for 12 months in most patients (Answer A is correct). Answer B is incorrect because 6 months of DAPT is only for patients at high risk of bleeding, and this patient has no indication of being at high risk of bleeding. No current data support DAPT indefinitely (Answer C is incorrect). Answer D is incorrect because the guidelines recommend DAPT for at least 12 months, not 18, in most patients.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: D

This patient has HFrEF (NYHA class III), probably secondary to her MI 4 months ago, and is not receiving optimal first-line HF therapy to reduce the risk of morbidity and mortality, making Answer A incorrect. Renin-angiotensin-aldosterone system blockade with an ARNI (or, alternatively, an ACEI or ARB) is considered a cornerstone of therapy for HFrEF because evidence shows that they slow the progression of HF and reduce symptoms, hospitalizations, and mortality in this patient population. These agents should be initiated in all patients with HFrEF, unless there is a contraindication. This patient has no contraindications for using an ARNI; therefore, sacubitril/valsartan should be initiated (Answer D). Digoxin is not indicated unless a patient is symptomatic on optimal HF therapy (Answer B). This patient is not symptomatic and is not receiving optimal therapy. Although the patient is NYHA class III, no rationale exists for adding vericiguat at this time because she is not receiving optimal HF therapy (Answer C).

2. Answer: C

This patient is taking the target dose of enalapril; further increases in the enalapril dose are unnecessary unless the patient is hypertensive (Answer B). Adding β-blocker therapy, initially at a low dose, together with ACE inhibitor therapy, is recommended for further reductions in morbidity and mortality and for slowing the progression of HF (Answer C). Digoxin is indicated only in symptomatic patients, despite optimal therapy, and this patient's pharmacotherapy has not been optimized, making Answers A and D incorrect.

3. Answer: D

This patient has HFpEF, which is caused by a problem with ventricular relaxation. Treatment of HFpEF includes managing risk factors such as HTN and optimizing HF pharmacotherapy. The most recent HF guidelines recommend consideration of SGLT2 inhibitors for patients with HFpEF and adequate renal function, making Answer D correct. SGLT2 inhibitors might result in slight reductions in the patient's blood pressure, but additional blood pressure control may be warranted in the future. Answer A is incorrect because the patient's heart rate is not elevated, and metoprolol succinate is not mortality reducing in HFpEF. Furosemide is not warranted because of lack of volume overload, making Answer B incorrect. Although spironolactone is an appropriate therapy for patients with HFpEF, especially in the context of HTN, this patient's potassium is greater than 5.0 mEq/L, so MRA therapy should not be initiated.

4. Answer: D

This patient's CHA_2DS_2-VASc score is 4 (risk factors are HTN, PAD, and age greater than 75 years), making him a candidate for an oral anticoagulant, such as rivaroxaban, because of his AF. Use of an oral anticoagulant will greatly decrease his risk of stroke from about 5% per year to about 1% per year. Because his HR is less than 110 beats/minute with atenolol therapy, there is no reason to discontinue atenolol. In addition, there is reason to add an additional rate control drug, such as digoxin (Answer B) or diltiazem (Answer A). With his PAD, atorvastatin therapy is necessary, making Answer C incorrect. In addition, his BP is well controlled; therefore, increasing the lisinopril dose is not warranted, making Answer B incorrect. To derive the beneficial antiplatelet effects for CV event prevention, aspirin 81 mg is adequate. Aspirin 325 mg/day is also effective, but has a greater risk of bleeding with concomitant apixaban. In fact, the most recent European Society of Cardiology guidelines recommend discontinuation of antiplatelets in the setting of full-dose DOACs; the ACC/AHA guidelines do not yet incorporate this recommendation. Therefore, adding apixaban and decreasing the dose of aspirin to 81 mg/day (Answer D) is the best answer.

5. Answer: A

This patient is experiencing a rapid ventricular response with exercise or strenuous activity, causing the sensation of palpitations and dyspnea. Digoxin alone poorly controls the ventricular rate during times of high sympathetic influence (e.g., exercise). Additional therapy is usually necessary to control the ventricular rate adequately. A β-blocker such as metoprolol succinate is a good choice to maintain HR during activity (Answer A). Using verapamil with digoxin in this patient could result in signs or symptoms of toxicity, given his current digoxin concentration. In addition, he is already taking a CCB, making verapamil a less desirable choice (Answer C). Similarly, doubling the digoxin dose would almost double the current serum concentration to 2.2 ng/dL, which should be avoided (Answer B). Instructing the patient to avoid activity is undesirable because physical activity should be encouraged and supported in all patients, especially in those with risk factors for CVD (Answer D).

6. Answer: C
According to the ACC/AHA guidelines, this patient's BP should be treated to a goal of less than 130/80 mm Hg because he has no clinical CVD and a 10-year ASCVD risk ≥10%, making answers B and D incorrect. Answers A and C both include appropriate medications for add-on therapy in HTN management. However, because of the patient's history of gout, losartan is likely a better choice because hydrochlorothiazide can cause uric acid buildup and potentially worsen gout. Therefore, Answer A is incorrect and Answer C is correct.

7. Answer: D
This patient has been identified as being at risk of ASCVD, according to his pooled cohort equation result of 14.6%. Therefore, the patient falls into one of the four patient management groups (age 40–75 years with an LDL-C of 70–189 mg/dL and a 10-year ASCVD risk of 7.5-19.9% without diabetes or ASCVD) and thus should be initiated on statin therapy. According to the guidelines, this patient should be treated with moderate- to high-intensity statin therapy. Although simvastatin 20 mg is considered a moderate-intensity dose, adding gemfibrozil to this patient's regimen would be inappropriate because gemfibrozil is contraindicated in combination with simvastatin; also, his TG concentrations are less than 500 mg/dL and need not be specifically targeted (Answer A). Using pravastatin 20 mg would be inappropriate because this is considered a low-intensity dose, and it would not provide the more than 30%–50% reduction in LDL-C that is recommended. In addition, fenofibrate would not be needed because his TG concentrations are lower than 500 mg/dL (Answer C). Rosuvastatin 2.5 mg is a low-intensity dose and would not be appropriate (Answer B). Atorvastatin 20 mg is considered a moderate-intensity dose, and it will provide a 30%-50% reduction in LDL-C, as is recommended (Answer D).

8. Answer: D
This patient is 40–75 years of age and does not have ASCVD, severe hypercholesterolemia, or diabetes. Therefore, he is in the statin treatment group of primary prevention. His 10-year ASCVD risk of 3.9% indicates he is considered at low risk. Statin therapy is not indicated at this time (Answers A and C are incorrect), and only lifestyle modifications are indicated. He should be reassessed in 4–6 years (Answer D is correct). The patient's TGs are normal, so treatment with a fibrate is not necessary at this time (Answer B is incorrect).

9. Answer: D
Secondary causes of hypertriglyceridemia should be ruled out when TG concentrations are greater than 500 mg/dL or when LDL-C is greater than 190 mg/dL. Different medications, conditions, and diet can affect these lipid values. Although obesity, poorly controlled diabetes, olanzapine, and metoprolol can increase TG concentrations, coenzyme Q does not affect TG; therefore, Answer A is incorrect. Alcohol consumption, poorly controlled diabetes, and β-blockers can all increase TG, but weight loss does not increase TG. Weight loss can actually lower LDL-C and TG; therefore, Answer B is incorrect. Although obesity and alcohol consumption can elevate TG, neither metformin nor hyperthyroidism is expected to have this effect (Answer C is incorrect). All the conditions, medications, or disease states in Answer D can increase TG, making this option correct.

10. Answer: D
Oral contraceptives, specifically estrogen, can increase BP, especially with a longer duration of use. An alternative contraceptive without estrogen would be less likely to contribute to her HTN (Answer D is correct). Answers A and B are incorrect because her BP requires better control, but weight loss is unlikely to help because her BMI is normal. Answer C is incorrect because hydrochlorothiazide is no more potent than chlorthalidone.

11. Answer: B
ACE inhibitor therapy is contraindicated in pregnancy, and discontinuing ramipril is the most important next step, making Answers A and C incorrect. Answer D is incorrect because this patient will require good BP control during her pregnancy. Labetalol is a good choice of therapy because it is a preferred antihypertensive drug in pregnancy (Answer B is correct).

12. Answer: D
Because the patient has CCD, his options for antiarrhythmic therapy are limited. Class Ic antiarrhythmic drugs are contraindicated in patients with CCD; therefore, flecainide and propafenone cannot be used (Answers B and C are incorrect). Disopyramide, a class Ia antiarrhythmic, is not a preferred therapy for AF; therefore, Answer A is incorrect. Sotalol, a class III antiarrhythmic, can be used in patients with CCD and good renal function; therefore, Answer D is correct.

Anticoagulation

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Anticoagulation

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Learning Objectives

1. Recommend a patient-specific pharmacotherapy plan to reduce the risk of stroke in patients with atrial fibrillation (AF).
2. Develop a feasible pharmacologic management plan to reduce thrombotic events in patients receiving aortic or mitral valve replacement.
3. Devise an evidence-based pharmacotherapy plan for the prevention and treatment of venous thromboembolism (VTE).
4. Analyze the need for anticoagulant therapy in patients with AF or VTE.
5. Determine appropriate reversal strategies for patients at risk of bleeding, or actively bleeding, while receiving anticoagulation therapy.
6. Determine appropriate selection and dosing of anticoagulant therapy on the basis of patient-specific factors and drug interactions.

Abbreviations in This Chapter

AF	Atrial fibrillation
CRNM	Clinically relevant nonmajor (bleeding)
DOAC	Direct oral anticoagulant
DVT	Deep vein thrombosis
INR	International normalized ratio
IPC	Intermittent pneumatic compression
LDUH	Low-dose unfractionated heparin
LMWH	Low-molecular-weight heparin
MI	Myocardial infarction
PCC	Prothrombin complex concentrate
4PCC	4-factor PCC
PCI	Percutaneous coronary intervention
PE	Pulmonary embolism
PRBC	Packed RBC
RBC	Red blood cell
TE	Thromboembolism
TTR	Time in therapeutic range
UFH	Unfractionated heparin
VKA	Vitamin K antagonist
VKOR	Vitamin K epoxide reductase
VTE	Venous thromboembolism

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

Questions 1–3 pertain to the following case.

J.M. is a 72-year-old female (weight 57 kg) who presents to the hospital with nonvalvular atrial fibrillation (AF). After her heart rate is controlled with metoprolol, she is asymptomatic. She also has hypertension, dyslipidemia, and depression. Her medications include metoprolol tartrate 100 mg orally twice daily, enalapril 10 mg orally twice daily, and citalopram 20 mg orally daily. Her heart rate is 78 beats/minute and blood pressure is 134/86 mm Hg. Her SCr is 0.8 mg/dL and CrCl is 60 mL/minute; she has normal hepatic function.

1. Which best depicts J.M.'s CHA_2DS_2-VASc score and HAS-BLED score?
   A. CHA_2DS_2-VASc score 1; HAS-BLED score 1.
   B. CHA_2DS_2-VASc score 3; HAS-BLED score 1.
   C. CHA_2DS_2-VASc score 5; HAS-BLED score 4.
   D. CHA_2DS_2-VASc score 3; HAS-BLED score 2.

2. Which is the most appropriate stroke prevention strategy for J.M.?
   A. Aspirin 325 mg orally once daily.
   B. Rivaroxaban 20 mg orally once daily.
   C. Apixaban 2.5 mg orally twice daily.
   D. Edoxaban 30 mg orally once daily.

3. J.M. was initiated on dabigatran and 3 months later is involved in a motor vehicle accident resulting in an intracranial hemorrhage. Which is the most appropriate reversal strategy for J.M.?
   A. Protamine.
   B. Fresh frozen plasma (FFP).
   C. Coagulation factor Xa [recombinant], inactivated.
   D. Idarucizumab.

Questions 4 and 5 pertain to the following case.

B.T. is 68-year-old male (height 183 cm, weight 96 kg) who recently underwent surgical aortic valve replacement with a bioprosthetic valve and is recovering well. He also has hypertension, dyslipidemia, systolic heart

failure, and a history of sustained ventricular tachycardia. His medications include carvedilol 25 mg orally twice daily, lisinopril 10 mg orally daily, furosemide 40 mg orally daily, amiodarone 400 mg orally daily, and atorvastatin 80 mg orally daily. His CrCl is 40 mL/minute, hepatic function is normal, and other laboratory data are within normal limits.

4. Which is the most appropriate antithrombotic regimen for B.T.?
   A. Aspirin 81 mg orally daily.
   B. Warfarin 7.5 mg orally daily to an INR of 2.5–3.5.
   C. Apixaban 5 mg orally twice daily.
   D. Dabigatran 150 mg twice daily.

5. Which best depicts how long B.T. should receive therapy?
   A. At least 1 month.
   B. At least 3 months.
   C. At least 1 year.
   D. Indefinitely.

Questions 6 and 7 pertain to the following case.
M.R. is a 51-year-old female (height 165 cm, weight 98 kg, BMI 36 kg/m^2) who presents to the ED with pain, swelling, and redness in her right leg up into her thigh. She also has some shortness of breath and pain in the middle of her chest. She reports that she had a hysterectomy about 2 weeks ago and has not been moving much at home in the past 2 weeks. On physical examination, her right leg is warmer than her left and tender to the touch. Her cardiac examination appears normal, with vital signs consisting of a heart rate of 80 beats/minute, blood pressure 146/96 mm Hg, respiratory rate 20 breaths/minute, and Sa_{O_2} 92% on room air. Her initial laboratory information includes a positive D-dimer, a negative troponin, and a CrCl of 65 mL/minute. Duplex ultrasound detects a right femoral-popliteal deep vein thrombosis (DVT), and CT reveals a pulmonary embolism (PE). Her other conditions include hypertension, type 2 diabetes, and dyslipidemia. She has also smoked 1 pack/day of cigarettes for the past 30 years. Her medications include lisinopril 10 mg orally daily, chlorthalidone 25 mg orally daily, metformin 1000 mg orally twice daily, pravastatin 40 mg orally daily, and hydrocodone 5 mg/acetaminophen 325 mg orally every 6 hours as needed for pain.

6. Which best depicts M.R.'s number of venous thromboembolism (VTE) risk factors?
   A. 3.
   B. 4.
   C. 5.
   D. 6.

7. Which is the most appropriate treatment strategy for M.R.?
   A. Enoxaparin 100 mg subcutaneously every 12 hours and dabigatran 150 mg orally twice daily; after 5 days, enoxaparin can be discontinued.
   B. Rivaroxaban 15 mg orally twice daily for 7 days, followed by 20 mg orally once daily.
   C. Enoxaparin 100 mg subcutaneously every 12 hours for 5 days; then initiate edoxaban 60 mg orally once daily.
   D. Unfractionated heparin (UFH) 4000-unit bolus, followed by 1000 units/hour and warfarin 7.5 mg orally daily to an INR of 2.0–3.0, discontinuing UFH when a therapeutic INR is reached.

8. A male patient (height 186 cm, weight 125 kg) is admitted for the treatment of a DVT with a PE. He is administered a 10,000-unit bolus of UFH and initiated on an infusion of 2000 units/hour. Twelve hours into the infusion, he begins to vomit blood. Which is the most appropriate protamine dose for this patient?
   A. 100 mg.
   B. 50 mg.
   C. 22.5 mg.
   D. 11.25 mg.

9. A female patient (height 163 cm, weight 65 kg) has undergone a hip fracture surgery. She has normal renal and hepatic function. Which is the most appropriate regimen for preventing VTE in this patient?
   A. Dabigatran 110 mg orally once 2 hours after surgery, followed by 220 mg orally once daily.
   B. Enoxaparin 30 mg subcutaneously once daily.
   C. Fondaparinux 2.5 mg subcutaneously once daily.
   D. Edoxaban 60 mg orally once daily.

BPS Pharmacotherapy Specialty Examination Content Outline

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline, tested during the Spring 2024 window:

1. Patient-Centered Pharmacotherapy
   a. 1.1. Develop patient-centered, evidence-based pharmacotherapy plans. Subtasks: 1.1.1–1.1.3, 1.1.5, 1.1.6, 1.1.8–1.1.12, 1.1.17
   b. 1.2. Monitor the patient to ensure safe and effective pharmacotherapy. Subtasks: 1.2.1–1.2.3
   c. 1.3. Modify pharmacotherapy plans through ongoing patient assessment. Subtasks: 1.3.1–1.3.4, 1.3.6, 1.3.7
2. Application of Evidence to Practice and Education
   a. 2.1. Retrieve relevant information that addresses pharmacotherapy-related inquiries. Subtask: 2.1.5
   b. 2.2. Evaluate pharmacotherapy-related literature and health information. Subtasks: 2.2.1, 2.2.3, 2.2.7

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline, tested starting Fall 2024:

1. Patient Care Specialty Areas
   a. 1A. Primary Pharmacotherapy Specialty Areas. Subtask: 1A2
   b. 1C. Tertiary Pharmacotherapy Specialty Areas. Subtask: 1C1
2. Therapeutics and Patient Management
   a. 2A. Treatment Planning. Subtasks: 2A1–2A5
   b. 2B. Therapeutic Implementation. Subtask: 2B1
   c. 2C. Treatment Outcomes and Monitoring. Subtasks: 2C1–2C4
3. Professional Practice
   a. 3A. Quality of Care. Subtasks: 3A3–3A5
   b. 3B. Evidence-Based Practice. Subtasks: 3B1, 3B3
   c. 3C. Practice Management. Subtask: 3C1

I. STROKE PREVENTION IN NONVALVULAR ATRIAL FIBRILLATION

A. Introduction
   1. Atrial fibrillation (AF) is the most common sustained cardiac dysrhythmia, affecting 2.7–6.1 million Americans. Overall prevalence of AF is 1%–2%.
   2. Incidence increases with advancing age.
      a. Around 1% of patients with AF are younger than 60.
      b. Around 12% of patients with AF are 75–84 years of age.
      c. More than 33% of patients with AF are 80 or older.
   3. AF accounts for more than 450,000 hospitalizations annually in the United States and significant health care costs.

B. Pathophysiology
   1. Etiology
      a. Typically related to structural heart disease such as coronary artery disease, valvular heart disease, heart failure, or other cardiogenic causes such as hypertension
      b. Noncardiogenic causes: Hyper- or hypothyroid disease, acute infection, excessive alcohol intake, after surgery, and pulmonary embolism (PE)
   2. Thrombosis
      a. Incomplete conduction of supraventricular impulses creates a lack of atrial contraction.
      b. Incomplete emptying of the cardiac chambers during systole increases the rate of blood pooling in the atria, most notably in the left atrial appendage.
      c. 90% of thromboses occur in the left atrial appendage and 10% in the left atrium.
      d. Blood stasis is associated with increased formation of mural thrombi, which may cause arterial embolization, or stroke, if dislodged by a return to normal sinus rhythm or by the shear forces from turbulent blood flow through the chambers.

C. In the 2019 focused update for the treatment of patients with AF from the American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS), the use of nonvalvular and valvular AF terminology was clarified because of confusion and varying definitions found in the AF literature. Therefore, the update has suggested use of the following definitions for related terms:
   1. Valvular AF is defined as AF in the presence of moderate to severe mitral stenosis or a mechanical heart valve.
   2. Nonvalvular AF refers to AF that excludes the valvular defects defined in valvular AF. This definition does not imply the absence of valvular heart disease in its entirety, given that direct oral anticoagulant (DOAC) trials enrolled a small percentage of patients with mild mitral stenosis, mitral or aortic regurgitation, aortic stenosis, tricuspid regurgitation, and/or valve repair, valvuloplasty, and bioprosthetic valves.

D. Stroke
   1. Nonvalvular AF increases the risk of stroke by 5-fold compared with patients without AF.
   2. AF is responsible for 15% of all strokes.
   3. Risk stratification (only for patients with nonvalvular AF)
      a. $CHADS_2$ score
         i. Maximum score of 6 based on risk factors (Table 1)
         ii. Risk of ischemic stroke is 1.9%–18.2%, depending on score (Table 2).
         iii. Limited by ability to determine who is truly at low or intermediate risk because scores of 0 or 1 suggest a risk of almost 2%–3% (see Table 2)

b. CHA_2DS_2-VASc score
   i. Maximum score of 9 based on risk factors (Table 1)
   ii. Compared with $CHADS_2$, adds risk factors of age 65–74, female sex, and history of other vascular disease
   iii. Improves predictive value of patients who are truly at low risk (score of 0 = 0% risk) and intermediate risk (score of 1 = 1.3% risk)
   iv. Guidelines from the AHA/ACC/HRS; European Society of Cardiology; and American College of Chest Physicians recommend using the CHA_2DS_2-VASc score to determine the need for anticoagulant therapy in patients without valvular AF (Table 3; Table 4).

Table 1. Risk Stratification for Ischemic Stroke in Patients with Nonvalvular Atrial Fibrillation

$CHADS_2$ Score		CHA_2DS_2-VASc Score	
Congestive heart failure[a]	1	Congestive heart failure[a]	1
Hypertension	1	Hypertension	1
Age ≥ 75	1	Age ≥ 75	2
Diabetes	1	Diabetes	1
Previous stroke, TIA, TE	2	Previous stroke, TIA, TE	2
		Vascular disease (prior MI, PAD, aortic plaque)	1
		Age 65–74	1
		Sex category (female)	1

[a]Heart failure as a risk factor represents patients with an ejection fraction ≤ 40%.
MI = myocardial infarction; PAD = peripheral artery disease; TE = thromboembolism; TIA = transient ischemic attack.

Table 2. Adjusted Stroke Rate per Year Based on $CHADS_2$ and CHA_2DS_2-VASc Scores

Score	$CHADS_2$ Adjusted Stroke Rate (%/yr)	CHA_2DS_2-VASc Adjusted Stroke Rate (%/yr)	Risk Category
0	1.9	0	Low
1	2.8	1.3	Intermediate
2	4.0	2.2	High
3	5.9	3.2	
4	8.5	4.0	
5	12.5	6.7	
6	18.2	9.8	
7	—	9.6	
8	—	6.7	
9	—	15.2	

Table 3. AHA/ACC/HRS Guideline Recommendations for Antithrombotic Therapy in Patients with Nonvalvular Atrial Fibrillation[a] Based on CHA_2DS_2-VASc Score

CHA_2DS_2-VASc Score of 0 in Men or 1 in Women	CHA_2DS_2-VASc Score = 1 in Men or 2 in Women	CHA_2DS_2-VASc Score ≥ 2 in Men or 3 in Women
Reasonable to omit anticoagulant therapy	May consider oral anticoagulation	Oral anticoagulant therapy is indicated. DOAC over warfarin in DOAC-eligible patients[a]

[a]Exclusions include moderate to severe mitral stenosis or mechanical heart valve.
DOAC = direct oral anticoagulant.

Table 4. AHA/ACC/HRS Guideline for the Treatment of Patients with AF[a]

Recommendation	Level of Evidence
Recommend assessment of stroke risk in patients without valvular AF using the CHA_2DS_2-VASc risk stratification tool	B
Oral anticoagulant therapy recommended for patients with AF and a CHA_2DS_2-VASc score ≥ 2 in men or ≥ 3 in women	A
Dabigatran (LOE: B), rivaroxaban (LOE: B), apixaban (LOE: B), and edoxaban (LOE: B-R) are recommended over VKA (e.g., warfarin) in eligible patients with AF	A
In patients with AF who have a mechanical heart valve, warfarin is the recommended oral anticoagulant	B
In patients treated with warfarin, an INR should be assessed at least weekly upon initiation and monthly when INR is stable (e.g., INR in range)	A
Selection of anticoagulation should be based on risk of TE and regardless of AF pattern (e.g., paroxysmal, persistent, or permanent)	B
In patients with nonvalvular AF who are unable to maintain a stable therapeutic INR with warfarin, use of a DOAC is recommended	C-EO
Patients with AF or atrial flutter ≥ 48 hr or unknown duration undergoing electrical or pharmacologic cardioversion should receive therapeutic anticoagulation with well-managed VKA (INR 2.0–3.0) or DOAC for at least 3 wk before and at least 4 wk after cardioversion regardless of CHA_2DS_2-VASc	B-R
Patients with AF ≥ 48 hr or unknown duration undergoing immediate cardioversion for hemodynamic instability should receive therapeutic anticoagulation as soon as possible and for at least 4 wk after successful cardioversion unless contraindicated	C
Regardless for AF of any duration, long-term anticoagulation therapy should be based on thromboembolic and bleeding risk profile after cardioversion	C-EO

[a]Recommendations listed only include those considered class I or strong by AHA/ACC/HRS.

AF = atrial fibrillation; DOAC = direct oral anticoagulant; INR = international normalized ratio; LOE = level of evidence; TE = thromboembolism; VKA = vitamin K antagonist.

c. HAS-BLED score (Table 5)
   i. 9-point scale to assess risk of major bleeding in patients being considered for anticoagulation
   ii. HAS-BLED score of 3 or greater indicates a high bleeding risk. It is estimated that less than 10% of patients have a score of 3 or greater.
   iii. Compared with other scoring systems (e.g., ATRIA or HEMORRHAGES), HAS-BLED more effectively discriminates risk.
   iv. Bleeding risk stratification with HAS-BLED should not be used to determine who does not receive therapy, but more to balance the risk of stroke with the risk of bleeding.
   v. Predictive value is inconsistent and unreliable with DOACs.

Table 5. Components and Bleeding Rates of the HAS-BLED Score

Risk Factors	Points
Hypertension (systolic blood pressure > 160 mm Hg)	1
Abnormal renal or liver function (1 point each)[a]	1 or 2
History of stroke	1
Bleeding tendency or predisposition[b]	1
Labile INRs[c] (for patients taking warfarin)	1
Older adults (age > 65)	1
Drugs or alcohol excess (1 point each)[d]	1 or 2
Score	**Risk of Major Bleeding/Year**
0	1.1%
1	1.0%
2	1.9%
3	3.7%
4	8.7%
5	12.5%
> 5	Undetermined

[a]Renal = chronic dialysis, renal transplantation, or SCr ≥ 2.26 mg/dL; liver = chronic hepatic disease (e.g., cirrhosis), bilirubin > 2 × the upper limit of normal (ULN), in association with AST/ALT/ALP > 3 × the ULN.

[b]History of bleeding or predisposition to bleeding such as anemia.

[c]Unstable/high INRs or time in therapeutic range < 60%.

[e]Drugs include antiplatelet drugs or nonsteroidal anti-inflammatory drugs; alcohol use is ≥ 8 alcoholic drinks/wk.

E. Anticoagulant Therapy
   1. Warfarin
      a. Vitamin K antagonist (VKA) – Racemic mixture of *S*- and *R*-isomers
         i. Inhibits vitamin K recycling by competitively inhibiting vitamin K epoxide reductase. Ultimately, this prevents the γ-carboxylation of clotting factors II, VII, IX, and X, leaving these factors to bind to phospholipid membranes and unable to take part in coagulation.
         ii. Also inhibits carboxylation and activation of natural anticoagulants, protein C and protein S
         iii. *S*-warfarin is about 4-fold more potent than *R*-warfarin.
      b. Several trials have shown a 70%–80% relative risk reduction in stroke and systemic embolism with warfarin therapy compared with placebo.
      c. Dosing for AF is based on requirements to achieve an INR goal of 2.0–3.0. Time to pharmacologic effect of warfarin requires consideration of the elimination half-life of inhibited clotting factors.
      d. Factor VII = 6 hours; factor IX = 24 hours; factor X = 36 hours; factor II = 72 hours. Functional clotting factors already activated must "run their course" and cannot be inhibited with higher doses, regardless of the INR.
      e. Initial starting dose is typically 5 mg orally daily, but doses of up to 10 mg daily may be required depending on patient-related factors (e.g., concomitant medication use that induces the metabolism of warfarin). A lower starting dose of 2–3 mg orally daily should be considered in patients with the following: advanced age, low body weight (less than 45 kg), drug interactions (e.g., inhibitors of warfarin metabolism), malnutrition, heart failure, hyperthyroid state, low albumin or liver disease, certain ethnic groups (e.g., Asian populations)
         i. In the outpatient setting, an INR should be measured at least weekly until the INR stabilizes.
         ii. Using pharmacogenomic data can achieve a faster therapeutic INR and fewer INRs of 4 or less but has not reduced thrombotic or bleeding events. Therefore, using pharmacogenomic data is not part of standard of care.

iii. In patients receiving a parenteral direct thrombin inhibitor or in lupus cases when the INR is not reflective of dosing, a factor VII or X concentration has been used with some success. A chromogenic factor X assay is likely most reliable for measuring the anticoagulant activity of warfarin in these patients, especially those with INR values greater than 3.0.

f. Follow-up INR monitoring
   i. INR values on a specific day are the result of warfarin doses taken over the previous 3–4 days, and dosing changes made on a specific day are not fully represented in the INR for 3–5 days. It takes 5–7 days to see the full effect of a stable warfarin dose.
   ii. If the INR is out of the therapeutic range in the outpatient setting, the total weekly dose should be increased or decreased by 5%–20%, depending on the INR; if the INR is greater than 4.0, the clinician should consider holding one or two doses before resuming the agent at a reduced maintenance dose.
   iii. If the INR was previously stable or therapeutic and a single out-of-range INR is 0.5 or less above or below the therapeutic range, current dosing can be continued; the INR should be rechecked within 1–2 weeks.
   iv. In general, there is no need to adjust dose if INR is within 0.1 of goal, but would monitor more closely (especially if below goal)
   v. If the INR decreases to 1.8 or less, the risk of ischemic stroke in AF increases by 60%, whereas the risk of bleeding does not significantly increase until the INR is greater than 4.0.
   vi. VKA therapy is well managed when the individual patient's time in therapeutic range (TTR) is greater than 65%–70%. If this level of TTR is not achieved, strategies should be implemented to improve the patient's TTR (e.g., more regular INR tests, education/counseling to better control diet, alcohol, drug interactions, medication adherence, or referral to a dedicated anticoagulation clinic).

g. Drug-drug interactions
   i. *S*-warfarin mainly metabolized by CYP2C9 > CYP3A4
   ii. *R*-warfarin mainly metabolized by CYP1A2, CYP3A4 > CYP2C19
   iii. Enzyme induction will produce a reduced INR and warfarin effect, increasing the risk of thrombosis (e.g., phenytoin, phenobarbital, carbamazepine, rifampin, St. John's wort).
   iv. Enzyme inhibition will produce an increased INR and warfarin effect, increasing the risk of bleeding.
      (a) *S*-warfarin – CYP2C9 > CYP3A4 (e.g., metronidazole, trimethoprim/sulfamethoxazole, fluconazole, isoniazid, fluoxetine, sertraline, amiodarone)
      (b) *R*-warfarin – CYP1A2 and CYP3A4 > CYP2C19 (e.g., clarithromycin, erythromycin, azole antifungals, fluoxetine, amiodarone, cyclosporine, sertraline, grapefruit juice, fluoroquinolones, protease inhibitors, diltiazem, verapamil, isoniazid, metronidazole)
   v. Pharmacodynamic effects with the concomitant use of antiplatelet agents (e.g., aspirin, $P2Y_{12}$ inhibitors, NSAIDs, fish oil, gingko, garlic)
   vi. Agents that compete for renal clearance (e.g., amiodarone, propafenone, cimetidine)
   vii. Agents that reduce vitamin K synthesis in the intestinal flora (e.g., antibiotics)
   viii. Agents that reduce warfarin absorption (e.g., cholestyramine, sucralfate)

h. Drug-disease interactions
   i. Increased clotting factor consumption (e.g., hyperthyroid state, fever)
   ii. Reduced warfarin metabolism (e.g., heart failure, liver disease, acute alcohol ingestion)
   iii. Increased warfarin metabolism (e.g., chronic alcohol ingestion, tobacco use)
   iv. Reduced clotting factor production (e.g., liver disease)
   v. Increased sensitivity to warfarin (e.g., acute infection, inflammation)

i. Drug-food interactions
    i. Consistent dietary intake of vitamin K is recommended because ingested vitamin K will bypass the vitamin K epoxide reductase inhibited by the VKA and reduce INR.
    ii. Wide variety of vitamin K in various food sources, with some green, leafy vegetables containing very high concentrations (greater than 200 mcg) of vitamin K (e.g., spinach, kale, collard greens, brussel sprouts, swiss chard)
    iii. In the setting of continuous enteral feeding, consider holding the feeds 1 hour before and after the dose to improve gastrointestinal absorption of warfarin.

2. Dabigatran
    a. Direct thrombin (IIa) inhibitor (Table 6)
    b. Recommended dosing: 150 mg orally twice daily. Reduced dose of 75 mg twice daily has not been evaluated in clinical trials. Reduced dose of 110 mg twice daily is not indicated for patients with AF in the United States but is used in Canada and Europe.
    c. Evaluated in the RE-LY trial compared with dose-adjusted warfarin: Dabigatran at a dose of 150 mg orally twice daily was associated with a significantly lower rate of stroke and systemic embolism with similar rates of major hemorrhage compared with warfarin. More precisely, events of life-threatening bleeding and intracranial hemorrhage were higher with warfarin; however, gastrointestinal bleeding occurred at a higher incidence with dabigatran 150 mg than with warfarin.
    d. In addition to bleeding, dyspepsia is a common adverse effect, occurring in about 10% of patients and contributing to significantly higher rates of drug discontinuation at 1 year and 2 years in the RE-LY trial.
    e. Drug interactions are based on P-glycoprotein (P-gp) (Table 7).
    f. Stability: Once the original packaging of dabigatran is opened, the medication should be used within 4 months to maintain appropriate potency, and capsules should remain stored in original container.
    g. Capsules should not be opened because this results in a 75% increase in bioavailability.
    h. See Box 1 for conversion to and from dabigatran to and from other anticoagulants.

Table 6. Direct Oral Anticoagulant Pharmacologic Properties

	Dabigatran	**Rivaroxaban**	**Apixaban**	**Edoxaban**
Mechanism of action	Direct IIa inhibitor	Factor Xa inhibitor	Factor Xa inhibitor	Factor Xa inhibitor
Bioavailability	3%–7%	66% without food, 80%–100% with food	50%	62%
Onset of anticoagulant activity (hr)	1–2	2–4	3–4	1–2
Half-life (hr)[a]	12–17	5–9	12	10–14
Renal clearance	80%	36%	27%	50%
Protein binding	35%	90%	87%	55%
Removed by dialysis	Yes	No	No	No
P-gp transport	Yes	Yes	Yes	Yes
Hepatic metabolism	None	CYP3A4/5 and CYP2J2	CYP3A4/5	Minimal (4% CYP3A4/5)

[a]Half-life can be increased in patients with advanced age and/or severe illness with renal and/or hepatic failure.
P-gp = P-glycoprotein.

Table 7. Dosing of DOACs in Atrial Fibrillation

Agent	Standard Dosing	Dose Adjustment[a]	Avoid Use[a]
Dabigatran	150 mg BID	75 mg BID • CrCl 15–30 mL/min • CrCl 30–50 mL/min with systemic ketoconazole or dronedarone (P-gp inhibitors)	• CrCl < 15 mL/min • Dialysis • CrCl 15–30 mL with amiodarone, verapamil, ketoconazole, dronedarone, and clarithromycin (P-gp inhibitors) • P-gp inducers (e.g., rifampin) • Chemotherapy agents – Vinblastine, doxorubicin, imatinib, crizotinib, vandetanib, sunitinib, abiraterone, and enzalutamide
Rivaroxaban	20 mg once daily with meals	15 mg once daily with meals • CrCl 15–50 mL/min • Dialysis[b]	• Strong CYP3A4 and P-gp inducers[c] • Strong CYP3A4 and P-gp inhibitors[d] • Chemotherapy agents – Vinblastine, doxorubicin, imatinib, crizotinib, vandetanib, sunitinib, abiraterone, and enzalutamide
Apixaban	5 mg BID	2.5 mg BID • Two of three criteria (age ≥ 80, weight ≤ 60 kg, or SCr ≥ 1.5 mg/dL) • Use with strong CYP3A4 and P-gp inhibitors[d] • Dialysis[b,e]	• Strong CYP3A4 and P-gp inducers[c] (e.g., rifampin, phenytoin, carbamazepine, St. John's wort) • If indicated for 2.5 mg BID and concomitant strong CYP3A4 and P-gp inhibitors[d] • Chemotherapy agents – Vinblastine, doxorubicin, imatinib, crizotinib, vandetanib, sunitinib, abiraterone, and enzalutamide
Edoxaban	60 mg once daily	30 mg once daily • CrCl 15–50 mL/min	• CrCl > 95 mL/min • CrCl < 15 mL/min • Dialysis • P-gp inducers (e.g., rifampin) • Chemotherapy agents – Vinblastine, doxorubicin, imatinib, crizotinib, vandetanib, sunitinib, abiraterone, and enzalutamide

[a]CrCl in the DOAC trials was calculated using the Cockcroft-Gault equation with total body weight.

[b]Data in the package label for dosing for rivaroxaban and apixaban in the setting of dialysis are from eight-patient, single-dose pharmacokinetic studies without available data supporting safety or efficacy.

[c]Strong CYP3A4 and P-gp inducers include rifampin, phenytoin, carbamazepine, St. John's wort.

[d]Strong CYP3A4 and P-gp inhibitors include protease inhibitors, itraconazole, ketoconazole, conivaptan.

[e]The apixaban package label suggests a dose of 5 mg BID in patients receiving dialysis with age < 80 and weight > 60 kg. A study with several days of apixaban administration in patients receiving dialysis showed about a 2-fold increase in Cmax and AUC using 5 mg BID and suggested that the 2.5-mg BID dose can be considered.

AUC = area under the curve; BID = twice daily; Cmax = peak concentration; CrCl = creatinine clearance; DOAC = direct oral anticoagulant; P-gp = P-glycoprotein..

Box 1. Dabigatran Conversion Strategies to and from Oral and Parenteral Anticoagulants

Converting from Dabigatran to Warfarin
Dependent upon calculated creatinine clearance (mL/min): • For patients with a CrCl ≥ 50 mL/min, initiate warfarin 3 days before discontinuing dabigatran • For patients with a CrCl 31–50 mL/min, initiate warfarin 2 days before discontinuing dabigatran • For patients with a CrCl 15–30 mL/min, initiate warfarin 1 day before discontinuing dabigatran • For patients with a CrCl < 15 mL/min, no dosing recommendations are available.
Converting from Warfarin to Dabigatran
Discontinue warfarin and initiate dabigatran when the INR is < 2.0[a]
Converting Between Dabigatran and Other Direct Oral Anticoagulants (DOACs)
Initiate the new DOAC at the time when the next dose of dabigatran was scheduled to be administered
Converting Between Dabigatran and Parenteral Anticoagulants
• Initiate dabigatran 0–2 hr before the next dose of the parenteral drug was to have been administered (e.g., LMWH) or when a continuously administered parenteral drug is discontinued (e.g., IV UFH) • For patients currently taking dabigatran, wait 12 hr (CrCl > 30 mL/min) or 24 hr (CrCl < 30 mL/min) after the last dose of dabigatran before initiating treatment with a parenteral anticoagulant

[a]Because dabigatran contributes to an increased INR, the INR will better reflect warfarin's effect after dabigatran has been discontinued for at least 2 days.

INR = international normalized ratio; IV = intravenous(ly); LMWH = low-molecular-weight heparin; UFH = unfractionated heparin.

3. Rivaroxaban
    a. Factor Xa inhibitor (see Table 6)
    b. Recommended dosing: 20 mg orally once daily with the evening meal. Reduced dose of 15 mg once daily is available and was used in around 20% of patients in the ROCKET-AF trial.
    c. Compared with dose-adjusted warfarin in the ROCKET-AF trial: Rivaroxaban was noninferior to warfarin for the prevention of stroke and systemic embolism and associated with a significantly reduced rate of intracranial hemorrhage and fatal bleeding.
    d. Drug interactions
        i. Strong CYP3A4 and P-gp inhibitors and inducers (see Table 7)
        ii. The package insert for rivaroxaban has a warning for use of moderate CYP3A4 and P-gp inhibitors (e.g., amiodarone, verapamil, diltiazem, erythromycin, dronedarone, cimetidine) in patients with a CrCl of 15–80 mL/minute due to risk for increased rivaroxaban concentrations, as demonstrated in pharmacokinetic studies. An analysis of patients receiving these agents with rivaroxaban with this level of renal function from the ROCKET-AF trials did not show an increased risk of bleeding.
    e. The absolute bioavailability of rivaroxaban is dose-dependent, reducing as the dose increases above 10 mg. Recommend that rivaroxaban 15 and 20 mg be administered with food to optimize oral bioavailability.
    f. See Box 2 for conversion to and from rivaroxaban to and from other anticoagulants.

Box 2. Rivaroxaban Conversion Strategies to and from Oral and Parenteral Anticoagulants

Converting from Rivaroxaban to Warfarin[a]
Discontinue rivaroxaban and initiate both a parenteral anticoagulant and warfarin when the next dose of rivaroxaban would have been taken. Discontinue the parenteral anticoagulant when INR > 2.0
Converting from Rivaroxaban to Anticoagulants Other than Warfarin
Discontinue rivaroxaban, and administer the first dose of the other anticoagulant (oral or parenteral; other than warfarin) when the next rivaroxaban dose would have been taken
Converting from Warfarin to Rivaroxaban[a]
Discontinue warfarin and initiate rivaroxaban once INR < 3.0
Converting from Anticoagulants Other than Warfarin to Rivaroxaban
Initiate rivaroxaban 0–2 hr before the next scheduled evening administration of the drug (e.g., LMWH or non-warfarin oral anticoagulant), and do not administer the other anticoagulant. For UFH administered by continuous infusion, discontinue the infusion and initiate rivaroxaban at the same time

[a]Because rivaroxaban contributes to INR, the INR measurement made during coadministration with warfarin may not accurately reflect the true value, complicating interpretation.

INR = international normalized ratio; LMWH = low-molecular-weight heparin; UFH = unfractionated heparin.

4. Apixaban
    a. Factor Xa inhibitor (see Table 6)
    b. Recommended dosing: 5 mg orally twice daily. Reduced dose of 2.5 mg twice daily is available and was used in about 5% of patients in the ARISTOTLE trial. Apixaban 2.5 mg orally twice daily was used in the landmark trial in individuals with two or more of the following: age 80 or older, weight 60 kg or less, and/or SCr 1.5 mg/dL or greater.
    c. Evaluated in the ARISTOTLE trial compared with dose-adjusted warfarin: Apixaban was associated with a significantly lower incidence of stroke, systemic embolism, major bleeding, hemorrhagic stroke, and death from any cause compared with warfarin.
    d. Drug interactions are associated with strong CYP3A4 and P-gp inhibitors and inducers (see Table 7).
    e. See Box 3 for conversion to and from apixaban to and from other anticoagulants.

Box 3. Apixaban Conversion Strategies to and from Oral and Parenteral Anticoagulants

Converting from Apixaban to Warfarin[a]
Discontinue apixaban, and initiate both a parenteral anticoagulant and warfarin when the next dose of apixaban would have been taken. Discontinue the parenteral anticoagulant when INR > 2.0
Converting from Apixaban to Anticoagulants Other than Warfarin
Discontinue apixaban, and initiate the new anticoagulant (oral or parenteral; other than warfarin) when the next dose would have been scheduled to be administered
Converting from Warfarin to Apixaban[a]
Warfarin should be discontinued and apixaban initiated when INR < 2.0
Converting from Anticoagulants Other than Warfarin to Apixaban
Discontinue the anticoagulant (e.g., LMWH or non-warfarin oral anticoagulant), and initiate apixaban at the usual time of the next dose of the anticoagulant. For UFH administered by continuous infusion, discontinue the infusion and initiate apixaban at the same time

[a]Because apixaban contributes to INR, the INR measurement made during coadministration with warfarin may not accurately reflect the true value, complicating interpretation. INR = international normalized ratio; LMWH = low-molecular-weight heparin; UFH = unfractionated heparin.

5. Edoxaban
    a. Factor Xa inhibitor (see Table 6)
    b. Recommended dosing: 60 mg orally once daily in patients with a CrCl between 50 and 95 mL/minute (see Table 6). Reduced dose of 30 mg once daily is available and was used in around 25% of the patients in the ENGAGE-AF TIMI 48 trial
    c. Evaluated in the ENGAGE-AF TIMI 48 trial compared with dose-adjusted warfarin: Edoxaban was noninferior to warfarin for the prevention of stroke or systemic embolism and associated with significantly lower rates of major bleeding and death from cardiovascular causes.
    d. Drug interactions are associated with P-gp (see Table 7).
    e. See Box 4 for conversion to and from edoxaban to and from other anticoagulants.

Box 4. Edoxaban Conversion Strategies to and from Oral and Parenteral Anticoagulants

Converting from Edoxaban to Warfarin
Oral option: For patients taking 60 mg of edoxaban, reduce the dose to 30 mg and initiate warfarin concomitantly. For patients receiving 30 mg of edoxaban, reduce the dose to 15 mg and initiate warfarin concomitantly. INR must be measured at least weekly and before the daily dose of edoxaban to minimize the influence of edoxaban on INR measurements. Once a stable INR ≥ 2.0 is achieved, edoxaban should be discontinued and warfarin continued Parenteral option: Discontinue edoxaban, and administer a parenteral anticoagulant and warfarin at the time of the next scheduled edoxaban dose. Once a stable INR ≥ 2.0 is achieved, the parenteral anticoagulant should be discontinued and warfarin continued
Converting from Edoxaban to Anticoagulants Other than Warfarin
Discontinue edoxaban, and initiate the new anticoagulant (oral or parenteral; other than warfarin) when the next dose would have been scheduled to be administered
Converting from Warfarin to Edoxaban
Discontinue warfarin and initiate edoxaban when the INR is ≤ 2.5
Converting from Anticoagulants Other than Warfarin to Edoxaban
Discontinue the other oral anticoagulant (other than warfarin) or LMWH, and initiate edoxaban at the usual time of the next dose of the other anticoagulant. For UFH administered by continuous infusion, discontinue the infusion and initiate edoxaban 4 hr later

INR = international normalized ratio; LMWH = low-molecular-weight heparin; UFH = unfractionated heparin.

6. DOAC vs. warfarin in AF
    a. Primary efficacy end point – stroke or systemic embolism (for all DOAC trials)
        i. All agents were noninferior to warfarin.
        ii. Dabigatran and apixaban were superior to warfarin in the intention-to-treat analysis.
        iii. Rivaroxaban and edoxaban were superior to warfarin in the per-protocol analysis.
    b. Hemorrhagic stroke – All agents showed a significantly lower rate of hemorrhagic stroke than warfarin. This is a key benefit of a DOAC over warfarin across all trials.
    c. Ischemic stroke – Dabigatran was the only DOAC that significantly reduced ischemic stroke at a dose of 150 mg orally twice daily, as shown in the unblinded RE-LY trial.
    d. Major bleeding
        i. Apixaban and edoxaban showed a statistically significant reduction in major bleeding compared with warfarin.
        ii. Dabigatran and rivaroxaban had safety outcomes similar to warfarin.
    e. All-cause mortality: All agents reduced mortality by approximately 10%, but apixaban was the only agent to show a statistically significant reduction in mortality compared with warfarin (p=0.01).

7. Controversies and considerations
    a. Major differences in the trials (Table 8) prevent concluding that one agent has superior efficacy or safety over any other. The AHA/ACC/HRS, European Society of Cardiology, and American College of Chest Physicians guidelines do not prefer one DOAC to another.
    b. Patient risk
        i. Varied results across the landmark trials evaluating the individual DOACs versus warfarin in AF may be the result of varying risks of enrolled study participants.
    c. TTR was greater than 60% in all trials except for ROCKET AF (55%). This trial had patients at the highest risk (mean $CHADS_2$ score 3.5) and was the only trial that did not provide the investigators with a protocol to follow for warfarin management because the study wanted to evaluate real-world practice. Regardless, analysis has shown that TTR with warfarin did not influence the study outcomes for any of the agents other than perhaps dabigatran.

Table 8. Comparison of Trial Characteristics of Direct Oral Anticoagulants vs. Warfarin

	RE-LY	ROCKET AF	ARISTOTLE	ENGAGE AF-TIMI 48
Study drug	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Study size	18,113 (three arms)	14,264 (two arms)	18,201 (two arms)	21,105 (three arms)
Double-blind	No	Yes	Yes	Yes
Previous VKA use (%)	50	62	57	59
$CHADS_2$ score				
Mean	2.1	3.5	2.1	2.8
0 or 1 (%)	32	0	34	—
2 (%)	36	13	36	77 (≤ 3)
3–6 (%)	32	87	30	23 (4–6)
Previous stroke or TIA (%)	20	55	19	28
Protocol to manage INR	Yes	No	Yes	Yes
Mean TTR (%)	64	55	62	65
Median TTR (%)	NR	58	66	68
Median follow-up (yr)	2.0	1.9	1.8	2.8

NR = not reported; TIA = transient ischemic attack; TTR = time in therapeutic range; VKA = vitamin K antagonist.

8. General precautions/warnings regarding DOACs and special populations:
    a. Because of limited safety or efficacy data in pregnancy, it is recommended to avoid DOACs.
    b. Evidence has confirmed the presence of DOACs in breast milk, or it is not known. In addition, safety data are limited; therefore, DOACs are not recommended for use in patients who are breastfeeding. An alternative mechanism of anticoagulation will be needed during breastfeeding.
    c. Avoid DOACs in patients with moderate to severe hepatic dysfunction (Child-Pugh class B or C) because of lack of data. These patients have been excluded from the phase III clinical trials.
    d. Avoid DOACs in patients with antiphospholipid syndrome.
        i. Two studies with DOACs showed worse clinical outcomes than with warfarin in patients with triple-positive antiphospholipid syndrome (lupus anticoagulant, anticardiolipin, and anti–β_2-glycoprotein I antibodies).
        ii. Although patients with single- or double-positive antiphospholipid syndrome were not included in these studies, it would be prudent to avoid DOACs until more data are available.
    e. Patients with obesity
        i. Although the use of DOACs was originally cautioned in patients with AF and class 3 (severe) obesity (BMI 40 kg/m^2 or greater) because of concern for potential underdosing of the anticoagulant, additional outcomes studies and post hoc analyses evaluating DOACs across BMI categories including class 3 obesity suggest maintenance of efficacy and safety of treatment.

ii. No dose adjustments are recommended when using apixaban, rivaroxaban, dabigatran, and edoxaban for AF on the basis of obesity status.
iii. Limited data suggest that even though dabigatran shows efficacy in patients with obesity (weight 120 kg or above), there is an increased risk of gastrointestinal (GI) bleeding. Use therapy with caution in this patient population.

f. Patients undergoing bariatric surgery: All DOACs have unpredictable pharmacokinetics in these patients and should therefore be avoided.
g. Patients with low body weight: Data are very limited, but are most supportive of apixaban and rivaroxaban, followed by edoxaban and dabigatran. Although no dose adjustment is recommended, these patients have an increase in concentration that may expose them to a higher risk of bleeding.

F. Patients with AF and Percutaneous Coronary Intervention (PCI)
1. Optimal antithrombotic therapy for patients with both AF requiring oral anticoagulation and PCI with stent(s) requiring dual antiplatelet therapy has been called "triple therapy" and deemed challenging in balancing efficacy in reducing complications such as stent thrombosis and stroke while minimizing risk of bleeding.
2. Although the risk of major bleeding with warfarin therapy in patients with AF is around 2% per year, patients receiving warfarin, aspirin, and clopidogrel ("triple therapy") have a major bleeding rate of around 8% per year.
3. Clinical approaches for patients with a need for both oral anticoagulants and antiplatelet therapy have been evaluated to reduce bleeding risk. Table 9 summarizes the landmark trials that support recommendations in the 2020 ACC expert consensus decision pathway and the 2023 AHA/ACC guideline for the treatment of patients with chronic coronary disease.

Table 9. Summarized Landmark Trials of Oral Anticoagulation and Antiplatelet Therapy for AF and PCI

Trial	WOEST	PIONEER AF-PCI	RE-DUAL PCI	AUGUSTUS	ENTRUST-AF PCI
Patients enrolled (n)	572	2124	2725	4614	1506
Inclusion criteria	Adults with indication for oral anticoagulant who underwent PCI	Adults with AF who underwent PCI	Adults with AF who underwent PCI	Adults with AF with recent ACS or PCI and planned use of $P2Y_{12}$ inhibitor for ≥ 6 mo	Adults with AF who underwent PCI
Follow-up (mo)	12	12	14	6	12
Treatment groups[a]	1. VKA + $P2Y_{12}$ inhibitor 2. VKA + aspirin + $P2Y_{12}$ inhibitor	1. Rivaroxaban (15 mg daily) + $P2Y_{12}$ inhibitor 2. Rivaroxaban (2.5 mg twice daily) + aspirin + $P2Y_{12}$ inhibitor 3. VKA + aspirin + $P2Y_{12}$ inhibitor	1. Dabigatran (110 mg twice daily) + $P2Y_{12}$ inhibitor 2. Dabigatran (150 mg twice daily) + $P2Y_{12}$ inhibitor 3. VKA + aspirin (1–3 mo) + $P2Y_{12}$ inhibitor	1. Apixaban (5 mg twice daily) + $P2Y_{12}$ inhibitor 2. Apixaban (5 mg twice daily) + aspirin + $P2Y_{12}$ inhibitor 3. VKA + $P2Y_{12}$ inhibitor 4. VKA + aspirin + $P2Y_{12}$ inhibitor	1. Edoxaban (60 mg daily) + $P2Y_{12}$ inhibitor 2. VKA + aspirin + $P2Y_{12}$ inhibitor
$P2Y_{12}$ inhibitor	Clopidogrel[b] (100%)	Clopidogrel[b] (93%) Ticagrelor[c] (5%) Prasugrel[d] (2%)	Clopidogrel[b] (88%) Ticagrelor[c] (12%)	Clopidogrel[e] (93%) Ticagrelor[e] (6%) Prasugrel[e] (1%)	Clopidogrel[b]
Primary outcome	Any bleeding	Clinically significant bleeding	Major bleeding or CRNM	Major bleeding or CRNM	Major bleeding or CRNM
Primary outcome event rate (HR; 95% CI)	19.4% vs. 44.4% (0.36; 0.26–0.5)	Group 1 vs. 3: 16.8% vs. 26.7% (0.59; 0.47–0.76) Group 2 vs. 3: 18% vs. 26.7% (0.63; 0.5–0.8)	Group 1 vs. 3: 15.4% vs. 26.9% (0.52; 0.42–0.63) Group 2 vs. 3: 20.2% vs. 25.7% (0.72; 0.58–0.88)	Apixaban vs. VKA: 10.5% vs. 14.7% (0.69; 0.58–0.81) Aspirin vs. placebo: 16.1% vs. 9% (1.89; 1.59–2.24)	17% vs. 20% (0.83; 0.65–1.05; p=0.001 for NI)

Table 9. Summarized Landmark Trials of Oral Anticoagulation and Antiplatelet Therapy for AF and PCI (*Cont'd*)

Trial	WOEST	PIONEER AF-PCI	RE-DUAL PCI	AUGUSTUS	ENTRUST-AF PCI
Primary ischemic/ thrombotic end point	Death, MI, stroke, target vessel revascularization, and stent thrombosis	Death from CV causes, MI, stroke	Death, MI, stroke, systemic embolism, or unplanned revascularization	Death or ischemic event (MI, stroke, stent thrombosis, revascularization)	Death from CV causes, stroke, systemic embolic event, MI, or stent thrombosis
Primary ischemic/ thrombotic event rate (HR; 95% CI)	11.1% vs. 17.6% (0.6; 0.38–0.94)	Group 1 vs. 3: 6.5% vs. 6% (1.08; 0.69–1.68) Group 2 vs. 3: 5.6 vs. 6% (0.93; 0.59–1.48)	Group 1 vs. 3: 15.2% vs. 13.4% (1.13; 0.9–1.43) Group 2 vs. 3: 11.8% vs. 12.8% (0.89; 0.67–1.19)	Apixaban vs. VKA: 6.7% vs. 7.1% (0.93; 0.75–1.16) Aspirin vs. placebo: 6.5% vs. 7.3% (0.89; 0.71–1.11)	7% vs. 6% (1.06; 0.71–1.69)

[a]Low-dose aspirin orally daily (75–100 mg).

[b]Clopidogrel dosing at 75 mg orally daily.

[c]Ticagrelor dosing at 90 mg orally twice daily.

[d]Prasugrel dosing at 10 mg orally once daily.

[e]Dosages not reported.

ACS = acute coronary syndrome; AF = atrial fibrillation; CRNM = clinically relevant nonmajor (bleeding); CV = cardiovascular; MI = myocardial infarction; NI = noninferiority; PCI = percutaneous coronary intervention; VKA = vitamin K antagonist.

4. Recommendations for antiplatelet therapy when oral anticoagulation is indicated
    a. Recommend against routine use of triple therapy
    b. Recommend a default strategy after PCI of an anticoagulant and a $P2Y_{12}$ inhibitor
        i. DOAC recommended over warfarin
        ii. Clopidogrel recommended over ticagrelor and prasugrel
    c. Durations after PCI (on the basis of ischemic and/or bleeding risk)
        i. Low/moderate ischemic/bleeding risk: May use dual antiplatelet therapy and anticoagulant for up to 30 days after PCI. Patients with low ischemic and high bleeding risk may consider continuing triple therapy for up to 7 days or until the day of discharge. If aspirin is used in combination with an anticoagulant, the dose should not exceed 100 mg orally daily.
        ii. PCI for stable ischemic heart disease: Patients should receive an anticoagulant and a $P2Y_{12}$ inhibitor for 6 months, then an anticoagulant alone long term.
        iii. PCI for an acute coronary syndrome should receive an anticoagulant and a $P2Y_{12}$ inhibitor for 12 months, then an anticoagulant alone.
        iv. Limiting use of antiplatelet therapy to only 3 months in patients receiving PCI for stable ischemic heart disease, or only 6 months in patients receiving PCI for an acute coronary syndrome, can be considered in patients at high risk of bleeding.
        v. For those with high ischemic risk (previous myocardial infarction, complex lesions, presence of cardiovascular disease, or extensive cardiovascular disease), consider triple therapy for 1 month, then discontinue aspirin and consider dual therapy with an anticoagulant and a $P2Y_{12}$ inhibitor for up to 6 months, then anticoagulant monotherapy thereafter.

Patient Case

Questions 1–4 pertain to the following case.

B.D. is a 73-year-old male (height 175 cm, weight 80 kg) with newly diagnosed nonvalvular AF. He also has a history of hypertension, dyslipidemia, stable ischemic heart disease, and systolic heart failure. His medications include aspirin 81 mg orally daily, enalapril 10 mg orally daily, atorvastatin 80 mg orally daily, metoprolol succinate 200 mg orally daily, furosemide 40 mg orally daily, spironolactone 25 mg orally daily, and amlodipine 10 mg orally daily. His heart rate is 72 beats/minute and blood pressure is 122/72 mm Hg. His laboratory values include K 4.9 mEq/L, stable SCr 1.9 mg/dL, and blood glucose 101 mg/dL.

1. Which best depicts B.D.'s CHA_2DS_2-VASc score?
   A. 2.
   B. 3.
   C. 4.
   D. 5.

2. Which is most accurate regarding DOAC therapy for reducing the risk of stroke in patients with nonvalvular AF such as B.D.?
   A. All the DOACs significantly reduced ischemic stroke in the phase III trials compared with warfarin.
   B. All the DOACs significantly reduced hemorrhagic stroke in the phase III trials compared with warfarin.
   C. Apixaban is more effective than rivaroxaban because apixaban was superior to warfarin in the ARISTOTLE trial and rivaroxaban was only noninferior to warfarin in the ROCKET-AF trial.
   D. Dabigatran was studied in patients with highest risk across the phase III trials and should not be used in patients with a $CHADS_2$ score less than 3.

3. Which is the most appropriate regimen for reducing B.D.'s risk of stroke?
   A. Dabigatran 75 mg orally twice daily.
   B. Rivaroxaban 20 mg orally once daily.
   C. Apixaban 5 mg orally twice daily.
   D. Edoxaban 60 mg orally once daily.

4. Six months later, B.D. elects to undergo PCI for the management of his chronic coronary artery disease. He has had no medication changes, and his vital signs and laboratory information remain consistent. Which is the best available evidence-based approach to B.D.'s antithrombotic therapy?
   A. Rivaroxaban 10 mg orally daily plus clopidogrel 75 mg orally daily.
   B. Apixaban 2.5 mg orally twice daily plus clopidogrel 75 mg orally daily.
   C. Adjusted-dose warfarin to an INR of 2.0–3.0 plus aspirin 81 mg orally daily plus clopidogrel 75 mg orally daily.
   D. Edoxaban 15 mg orally once daily plus aspirin 81 mg orally daily plus clopidogrel 75 mg orally daily.

II. ANTICOAGULATION IN VALVULAR HEART DISEASE

A. Risk of thromboembolism (TE) can be 20-fold higher for patients with valve disease than for patients without this disease.

B. The 2020 ACC/AHA guidelines on the management of valvular disease provide the most up-to-date information on the role of anticoagulation with valvular heart disease.

C. Bioprosthetic Heart Valves
   1. The first 3 months is the highest-risk period of TE after bioprosthetic heart valve implantation, especially with mitral valves.
   2. Bioprosthetic heart valves have a lower long-term risk of TE than mechanical heart valves.
   3. Risk of TE is higher with mitral valves than with aortic valves because of the larger diameter and therefore slower flow of the mitral valve compared with the smaller diameter and faster flow of the aortic valve.
   4. Surgical aortic bioprosthetic valve
      a. Lifelong low-dose aspirin (75–100 mg orally daily) for patients without another indication for oral anticoagulation (class 2a recommendation)
      b. Patients at low risk of bleeding can receive initial anticoagulation with warfarin to a target INR of 2.5 (±0.5) for at least 3 months and for up to 6 months (class 2a recommendation).
   5. Transcatheter aortic valve implantation
      a. Lifelong low-dose aspirin (75–100 mg orally daily) for patients without another indication for oral anticoagulation (class 2a recommendation)
      b. Patients at low risk of bleeding may receive initially one of the following for 3–6 months (class 2b recommendation):
         i. Low-dose aspirin (75–100 mg) orally daily and clopidogrel 75 mg orally daily
         ii. Warfarin at a target INR of 2.5 (±0.5)
   6. Mitral bioprosthetic valve
      a. Lifelong low-dose aspirin for patients without another indication for oral anticoagulation (class 2a recommendation)
      b. Patients at low risk of bleeding can receive warfarin to a target INR of 2.5 (±0.5) for at least 3 months and for up to 6 months (class 2a recommendation).
   7. Patients with concomitant AF
      a. If bioprosthetic valve placement was more than 3 months ago, a DOAC is an effective alternative to warfarin, and use should be based on the patient's CHA_2DS_2-VASc score (class 1 recommendation).
      b. If AF onset is within 3 months of bioprosthetic valve placement, warfarin should be used. Optimal duration of anticoagulation is not well defined. Repeat evaluation for recurrence of arrythmia is recommended, and evaluation of CHA_2DS_2-VASc score is encouraged (class 2a recommendation).
         i. The RIVER trial (n=1005) evaluated rivaroxaban 20 mg daily and warfarin (INR 2.0–3.0) in patients with AF and a bioprosthetic mitral valve.
         ii. Rivaroxaban was noninferior to warfarin (median TTR of 65.5%) with respect to the mean time until the primary outcome of death, major CV events, or major bleeding at 12 months.
         iii. Thrombotic events or CV death with rivaroxaban was 3.4% compared with 5.1% with warfarin (HR 0.65; 95% CI, 0.35–1.20).
         iv. Stroke was significantly lower with rivaroxaban (0.6% vs. 2.4%). Major bleeding with rivaroxaban was 1.4% compared with 2.6% with warfarin (HR 0.54; 95% CI, 0.21–1.35).
         v. In the 20% of patients enrolled within 3 months of valve placement, thrombotic events or CV death was significantly reduced with rivaroxaban compared with warfarin (6.4% vs. 18.9%), suggesting a role for use of a DOAC within the first 3 months of valve placement.

D. Mechanical Heart Valves
   1. Warfarin therapy should be used regardless of the valve position to prevent valve thrombosis and TE events (class 1 recommendation).
   2. Aortic mechanical heart valve
      a. Patients with a bileaflet or current-generation single-tilting disk valve and no risk factors for TE should have a target INR of 2.5 (±0.5) (class 1 recommendation).
      b. Patients with risk factors for TE (i.e., AF, prior TE, left ventricular systolic dysfunction, hypercoagulable state) or those with an older-generation valve (e.g., ball-in-cage) should have a target INR of 3.0 (±0.5) (class 1 recommendation).
      c. Low-dose aspirin should only be added for patients with an indication for antiplatelet therapy and a low risk of bleeding (class 2b recommendation).
      d. Patients receiving an On-X aortic valve and having no risk factors for TE should have a target INR of 2.5 (±0.5) for the first 3 months, followed by a target INR of 1.5–2.0 with low-dose aspirin (class 2b recommendation).
   3. Mitral mechanical heart valve
      a. Patients should receive warfarin therapy with a target INR of 3.0 (±0.5) (class 1 recommendation).
      b. Low-dose aspirin should only be added for patients with an indication for antiplatelet therapy and a low risk of bleeding (class 2b recommendation).
   4. Aortic and mitral heart valves – Patients should receive warfarin therapy with a target INR of 3.0 (±0.5).
   5. Bridging therapy
      a. After mechanical valve placement, patients should receive bridge therapy with an injectable anticoagulant for at least 5 days and should have an INR within the therapeutic range before the parenteral anticoagulant is discontinued.
      b. For patients with mechanical heart valves undergoing a minor procedure (e.g., dental extraction or cataract removal) in which bleeding is easily controlled, warfarin should be continued with a therapeutic INR (class 1 recommendation).
      c. For patients with a bileaflet mechanical aortic valve and no other risk factors for TE undergoing an invasive procedure and a temporary interruption of warfarin, no bridging is needed while the INR is subtherapeutic (class 1 recommendation).
      d. For patients undergoing an invasive procedure with a mechanical aortic valve with risk factors for TE, an older-generation mechanical aortic valve, or a mechanical mitral valve, bridging anticoagulant therapy while the INR is subtherapeutic is reasonable, with the risk of bleeding weighed against the risk of thrombosis (class 2a recommendation).

Patient Case

Questions 5 and 6 pertain to the following case.

S.D. is a 62-year-old female (height 165 cm, weight 80 kg) with a history of significant primary mitral regurgitation. Her echocardiogram reveals significant leaflet flaring that is not amendable to mitral valve repair. She also has a history of hypertension, dyslipidemia, and gout. Her medications include lisinopril 10 mg orally daily, hydrochlorothiazide 25 mg orally daily, simvastatin 40 mg orally daily, and allopurinol 300 mg orally daily. Her heart rate is 68 beats/minute and blood pressure is 128/74 mm Hg. Her CrCl is 68 mL/minute. She is scheduled to undergo valve replacement surgery and will receive a mechanical mitral valve. You are discussing the oral anticoagulant postoperative plan with S.D.'s team.

5. Which is the optimal regimen for preventing thrombosis?
   A. Adjusted-dose warfarin to an INR goal of 2.5–3.5 plus aspirin 81 mg orally daily.
   B. Adjusted-dose warfarin to an INR goal of 2.0–3.0 plus aspirin 81 mg orally daily.
   C. Adjusted-dose warfarin to an INR goal of 2.0–3.0.
   D. Adjusted-dose warfarin to an INR goal of 2.5–3.5.

6. Which best describes thrombotic risk in patients with valve replacement surgery?
   A. Bioprosthetic valves carry a higher risk of thrombosis than mechanical valves.
   B. The highest risk of thrombosis with bioprosthetic valve placement is during the first year after surgery.
   C. All patients with mechanical heart valves require bridging therapy during invasive procedures.
   D. Valve replacement in the mitral position carries a higher risk of thrombosis than in the aortic position.

III. PREVENTION OF VENOUS THROMBOEMBOLISM

A. Risk of Developing VTE
   1. VTE consists of a deep vein thrombosis (DVT), a PE, or both.
   2. Box 5 lists risk factors for developing VTE. Risk factors are cumulative.
      a. Not all risk factors carry equal risk; patients with certain risk factors such as orthopedic surgery, trauma, cancer, certain hypercoagulable states, and a previous VTE have the highest risk of developing VTE.
      b. Table 10 lists risks of VTE according to different patient groups. These event rates have typically been determined by venography in clinical trials and do not reflect the rates of symptomatic DVT or PE.
   3. Risk stratification
      a. Low risk (DVT incidence less than 10% without thromboprophylaxis)
         i. Minor surgery in patients younger than 40 with no additional risk factors
         ii. Medically ill patients who are fully mobile
      b. Moderate risk (DVT incidence 10%–40% without thromboprophylaxis)
         i. In general, patients undergoing open gynecologic or urologic surgery
         ii. Medically ill patients, patients with need for bed rest
      c. High risk (DVT incidence 40%–80% without thromboprophylaxis)
         i. Major surgery in patients older than 40 plus a prior VTE
         ii. Cancer
         iii. Hypercoagulable state
         iv. Hip or knee arthroplasty, hip fracture surgery
         v. Major trauma
         vi. Spinal cord injury

4. Prophylactic regimens vary depending on patient risk and clinical trial results.
    a. Mechanical prophylaxis
        i. Includes graduated (elastic) compression stocking (limited efficacy) and intermittent pneumatic compression (IPC)
        ii. IPC must be on the patient for at least 18 hours/day to demonstrate efficacy.
        iii. Both types of mechanical prophylaxis are poorly tolerated by patients.
        iv. Appropriate in patients at high risk of bleeding, such as immediately after surgery, with intent to substitute pharmacologic prophylaxis once hemostasis has occurred
        v. Also, may be used in patients at highest risk, such as those with spinal cord injury, in combination with pharmacologic prophylaxis
    b. Pharmacologic prophylaxis
        i. Low-molecular-weight heparin (LMWH) – Subcutaneous enoxaparin or dalteparin
        ii. Low-dose UFH (LDUH) – Subcutaneously twice daily or three times daily
        iii. Fondaparinux – Subcutaneously daily
        iv. Warfarin – adjusted-dose to target INR – in orthopedic surgery
        v. DOACs – Dabigatran, rivaroxaban, and apixaban – in orthopedic surgery; rivaroxaban – for extended prophylaxis in the medically ill
        vi. Aspirin – Questionable data, but listed as a possible agent in orthopedic surgery

Box 5. Risk Factors for Developing VTE

Age ≥ 40
Surgery (e.g., orthopedic, thoracic, abdominal, and genitourinary)
Trauma (e.g., fracture of the spine, pelvis, femur, or tibia; spinal cord injuries)
Hypercoagulable states (e.g., resistance to activated protein C [factor V Leiden], deficiencies in antithrombin, protein C or protein S, antiphospholipid antibodies
Central venous catheterization
Estrogen use or selective estrogen receptor modulators
Erythropoiesis-stimulating agents
Previous VTE
Cancer and its treatment (e.g., pancreas, lung, ovary, testes, urinary tract, breast, stomach)
Immobility or lower extremity paresis
Certain medical disease states/conditions (e.g., stroke, or paralysis, acute infection, chronic obstructive pulmonary disease, inflammatory bowel disease, nephrotic syndrome, varicose veins, heart failure, acute MI, pregnancy)
Smoking
Obesity

MI = myocardial infarction; VTE = venous thromboembolism.

Table 10. Venous Thromboembolism Risk in Different Hospitalized Patient Groups

Patient Group	Deep Vein Thrombosis Prevalence Without Prophylaxis (%)
Medically ill patients Heart failure Chronic obstructive pulmonary disease Infection	10–20
Critical care patients	10–20
General surgery	15–40
Major gynecologic surgery	15–40
Major urologic surgery	15–40
Neurosurgery	15–20
Stroke	20–50
Major orthopedic surgery Total hip replacement surgery Hip fracture surgery Total knee replacement surgery	40–60 57 60 84
Major trauma	40–80
Patients with spinal cord injury	60–80

B. Orthopedic Surgery
   1. Typically considered one of the highest-risk settings for developing VTE
      a. More than 50% of patients have a VTE event without prophylaxis.
      b. DVT rates are higher in knee surgery, and PE rates are higher in hip surgery.
   2. Throughout the hospital stay, both mechanical prophylaxis with IPC and pharmacologic prophylaxis are recommended.
   3. American College of Chest Physicians guidelines: Pharmacologic prophylaxis of VTE in orthopedic surgery (Table 11)
      a. Total knee arthroplasty: LMWH, fondaparinux, apixaban, rivaroxaban, dabigatran, adjusted-dose warfarin, LDUH, aspirin
      b. Total hip arthroplasty: LMWH, fondaparinux, apixaban, rivaroxaban, dabigatran, adjusted-dose warfarin, LDUH, aspirin
      c. Hip fracture surgery: LMWH, fondaparinux, dose-adjusted warfarin, aspirin
   4. See Table 11 for prophylactic dosing regimens.
   5. Duration of prophylactic treatment: At least 10–14 days of pharmacologic prophylaxis; however, extended prophylaxis of 35 days is suggested, especially in hip replacement or fracture surgery
   6. Practical issues
      a. LDUH (5000 units every 8–12 hours) has consistently shown insufficient protection against VTE in patients undergoing orthopedic surgery and should therefore not be considered an acceptable alternative.
      b. Although aspirin 81 mg orally daily has a recommendation from the American Society of Hematology (ASH), the American College of Chest Physicians, and the American Academy of Orthopaedic Surgeons guidelines for use as postoperative prophylaxis in patients who have undergone total hip or knee arthroplasty, it is based on limited data with several limitations.

c. Patients placed on mechanical prophylaxis after surgery because of a high risk of bleeding should have their risk of bleeding consistently reassessed, with pharmacologic prophylaxis initiated as soon as the bleeding risk is decreased.
d. Patients undergoing knee arthroscopy typically do not need VTE prophylaxis beyond early mobilization unless they have additional VTE risk factors or have a complicated procedure. In those cases, patients should receive VTE prophylaxis with a DOAC or LMWH.
e. Dalteparin (LMWH) has shown rates of VTE similar to enoxaparin 40 mg once daily in hip replacement surgery.
    i. Heterogeneity in studies comparing dalteparin with enoxaparin in those undergoing knee replacement surgery exists. One trial showed that dalteparin was inferior to enoxaparin 30 mg twice daily for the primary composite outcome of VTE and death.
    ii. Dalteparin was inferior to enoxaparin 30 mg twice daily in patients undergoing knee replacement surgery.
f. Rivaroxaban has shown a superior reduction in VTE events compared with enoxaparin 40 mg once daily in hip replacement surgery and enoxaparin 40 mg once daily and enoxaparin 30 mg twice daily in knee replacement surgery. Although major bleeding was not significantly increased in these studies, the definition of major bleeding did not include surgical site bleeding (considered nonmajor bleeding).
g. Apixaban has shown a superior reduction in VTE events compared with enoxaparin 40 mg once daily in hip replacement surgery, with no significant increase in major bleeding. Apixaban did not meet the statistical criteria for noninferiority when compared with enoxaparin 30 mg twice daily in knee replacement surgery, though the event rates were similar (9.0% apixaban vs. 8.8% enoxaparin). Although there was no difference in major bleeding, the combination of major and clinically relevant nonmajor (CRNM) bleeding was significantly reduced with apixaban.
h. Timing of initiation of VTE prophylaxis after surgery is an important and complicated issue. The risk of thromboembolic events begins immediately after surgery; therefore, VTE prophylaxis is usually more effective when initiated earlier instead of later. The challenge is that early VTE prophylaxis is also associated with increased bleeding compared with VTE prophylaxis initiated later.
i. VTE prophylaxis after elective spinal surgery can typically be initiated 12–24 hours after the operation. Prophylaxis may need to be delayed if the surgical site remains open.

Table 11. VTE Prophylaxis in Orthopedic Surgery

Orthopedic Indication	Enoxaparin	Dalteparin	Fondaparinux	Warfarin	Dabigatran	Rivaroxaban	Apixaban
Knee replacement surgery	30 mg SC q12hr initiated 12–24 hr after surgery	2500 units SC administered 6–8 hr after surgery; then 5000 units SC q24hr[a]	2.5 mg SC q24hr initiated 6–8 hr after surgery	Initiated preoperatively or the evening of the surgical day with adjusted dosing to achieve a target INR of 2.5 (±0.5)	110 mg PO initiated 1–4 hr after surgery; then 220 mg PO once daily[a,b]	10 mg PO once daily initiated 6–10 hr after surgery[c]	2.5 mg PO BID, initiated 12–24 hr after surgery
Hip replacement surgery	30 mg SC q12hr initiated 12–24 hr after surgery OR 40 mg SC q24hr initiated 12 (±3) hr before surgery	2500 units SC administered 4–8 hr after surgery; then 5000 units SC q24hr OR 5000 units SC q24hr initiated the evening before surgery	2.5 mg SC q24hr initiated 6–8 hr after surgery	Initiated preoperatively or the evening of the surgical day with adjusted dosing to achieve a target INR of 2.5 (±0.5)	110 mg PO initiated 1–4 hr after surgery; then 220 mg PO once daily[b]	10 mg PO once daily initiated 6–10 hr after surgery[c]	2.5 mg PO BID, initiated 12–24 hr after surgery

Table 11. VTE Prophylaxis in Orthopedic Surgery *(Cont'd)*

Orthopedic Indication	Enoxaparin	Dalteparin	Fondaparinux	Warfarin	Dabigatran	Rivaroxaban	Apixaban
Hip fracture surgery	30 mg SC q12hr initiated 12–24 hr after surgery[a]; 40 mg SC q24hr initiated 12 (±3) hr before surgery	Insufficient evidence	2.5 mg SC q24hr initiated 6–8 hr after surgery	Initiated preoperatively or the evening of the surgical day with adjusted dosing to achieve a target INR of 2.5 (±0.5)	Insufficient evidence	Insufficient evidence	Insufficient evidence
Spinal surgery	Mechanical prophylaxis using IPC is preferred to pharmacologic prophylaxis unless the patient is considered at high risk of VTE. If the patient has additional risk factors, including advanced age, malignancy, neurologic deficit, prolonged immobility, previous VTE, or an anterior-posterior surgical approach, LMWH or LDUH is suggested						

[a]Not FDA approved.

[b]CrCl > 30 mL/min.

[c]CrCl ≥ 15 mL/min.

BID = twice daily; IPC = intermittent pneumatic compression; LDUH = low-dose unfractionated heparin; LMWH = low-molecular-weight heparin; PO = oral(ly); q = every; SC = subcutaneous(ly); VTE = venous thromboembolism.

C. Non-orthopedic Surgery

1. Consists of a heterogeneous group of patients and surgical procedures with varying risk. Risk assessment models such as Caprini may be used to assess VTE risk and, subsequently, indication for pharmacologic prophylaxis in patients undergoing general, non-orthopedic or abdominal-pelvic surgery. Table 12 shows a detailed Caprini risk assessment model. Table 13 describes association of VTE risk with recommendations for pharmacologic and/or mechanical prophylaxis according to the 2012 American College of Chest Physicians guidelines.
2. Pharmacologic prophylaxis, when indicated, may include LMWH or LDUH. Table 14 lists prophylactic dosing regimens.
3. Risk factors for major bleeding for patients undergoing general non-orthopedic surgery include active bleed; history of major bleed; known and untreated bleeding disorder; severe renal or hepatic failure; thrombocytopenia; acute stroke; uncontrolled hypertension; concomitant use of anticoagulants, antiplatelets, or thrombolytic drugs; and lumbar puncture, epidural, or spinal anesthesia within the previous 4 hours or next 12 hours.
4. The 2012 American College of Chest Physicians guidelines further elaborate on indications for pharmacologic prophylaxis for patients undergoing cardiac, thoracic, craniotomy, spinal, and surgical procedures related to major traumas. If indicated, LMWH or LDUH will be favored for pharmacologic prophylaxis. See Table 14 for details on prophylactic dosing regimens.

Table 12. Caprini Risk Assessment for VTE in General Non-orthopedic or Abdominal Pelvic Surgery

Caprini Points	Associated Risk Factors
1	Age 41–60 BMI > 25 kg/m^2 Minor surgery or history of major surgery (< 1 mo ago) Certain medications (OCPs, HRT) Pregnancy or postpartum Swollen or varicose veins in the legs History of unexplained or recurrent spontaneous abortion Sepsis (< 1 mo ago) History of IBD Acute MI Congestive heart failure (< 1 mo ago) Serious lung disease or abnormal pulmonary function (e.g., pneumonia < 1 mo ago) Medical patient on bed rest
2	Age 61–74 Arthroscopic surgery Major open surgery (> 45 min in duration) Laparoscopic surgery (> 45 min in duration) Malignancy Immobility (bed confinement > 72 hr) Immobilizing plaster cast Central venous access
3	Age ≥ 75 Personal or family history of VTE Inherited/acquired hypercoagulable conditions (e.g., factor V Leiden, lupus anticoagulant, prothrombin G20210A, presence of anticardiolipin antibodies) Elevated serum homocysteine HIT Other congenital or acquired thrombophilia
5	Stroke (< 1 mo ago) Elective arthroplasty Hip, pelvis, or leg fracture Acute spinal cord injury or recent multiple traumas (< 1 mo ago)

HIT = heparin-induced thrombocytopenia; HRT = hormone replacement therapy; IBD = inflammatory bowel disease; MI = myocardial infarction; OCP = oral contraceptive pill; VTE = venous thromboembolism.

Table 13. VTE Prophylaxis for Patients Undergoing General Non-orthopedic or Abdominal-Pelvic Surgery

VTE Risk	VTE Risk (%)	Caprini Score	Average Bleeding Risk (~1%)	High Bleeding Risk (~2%)
Very low	< 0.5	0	Early ambulation	
Low	1.5	1 or 2	Mechanical prophylaxis (IPC preferred)	
Moderate	3	3 or 4	LMWH, LDUH, or IPC	Mechanical prophylaxis (IPC preferred)
High	6	≥ 5	LMWH, LDUH **AND** IPC	IPC Add LMWH or LDUH once bleeding risk diminishes
High (cancer surgery)	—	N/A	LMWH or LDUH **AND** IPC (extended-duration prophylaxis with LMWH upon discharge)	IPC Add LMWH or LDUH once bleeding risk diminishes
High risk *(LMWH or LDUH contraindicated or unavailable)*	—	N/A	Low-dose aspirin (160 mg) or fondaparinux **AND** IPC	IPC Add low-dose aspirin (160 mg) or fondaparinux once bleeding risk diminishes

IPC = intermittent pneumatic compression; LDUH = low-dose unfractionated heparin; LMWH = low-molecular-weight heparin; N/A = not applicable; VTE = venous thromboembolism.

5. Practical issues
    a. General surgery
        i. Meta-analysis comparisons between LDUH and LMWHs show similar efficacy in preventing DVT but a greater reduction in the incidence of PE when LMWH is used.
        ii. Mechanical prophylaxis is sometimes inappropriately selected over pharmacologic prophylaxis because of concerns for bleeding in surgical patients. A meta-analysis of almost 34,000 surgical patients showed that the most common bleeding complications were injection-site bruising (6.9%) and wound hematomas (5.7%). Major bleeding complications occurred in less than 1% of patients.
    b. Neurosurgery
        i. Pharmacologic prophylaxis is typically administered with mechanical prophylaxis, and the combination is as safe as, and more effective than, mechanical prophylaxis alone.
        ii. Pharmacologic prophylaxis is typically initiated 18–24 hours after neurosurgery.
    c. Vascular surgery
        i. Routine prophylaxis is recommended for patients with additional risk factors such as advanced age, limb ischemia, long duration of surgery, and intraoperative local trauma.
        ii. Because of the few trials of patients undergoing vascular surgery, dosing recommendations are based on evidence for pharmacologic agents in general surgery.
    d. Gynecologic surgery
        i. Low-risk gynecologic surgical procedures (laparoscopic procedures or procedures lasting less than 30 minutes) do not require prophylaxis beyond early ambulation.
        ii. Those undergoing major surgery without malignancy should receive LDUH or LMWH.

e. Gynecologic cancer surgery
   i. LDUH administered three times daily is more effective than twice daily. LDUH dosed three times daily and LMWH have similar efficacy and safety.
   ii. In a subgroup analysis of a general surgery trial, fondaparinux was more effective than dalteparin in patients undergoing surgery for cancer.
f. Urologic surgery
   i. Patients undergoing a transurethral or laparoscopic urologic procedure do not require prophylaxis beyond early ambulation.
   ii. Because of the few trials of patients undergoing urologic surgery, dosing recommendations are based on the evidence for pharmacologic agents in general surgery.
g. Bariatric surgery: Higher doses of LMWH and LDUH are recommended. LDUH 7500 units three times daily for individuals with a BMI greater than 50 kg/m^2 and enoxaparin 40 mg twice daily for individuals with a BMI of 40 kg/m^2 or greater have been evaluated. Dalteparin 7500 units daily has been evaluated in a retrospective study using anti-Xa concentrations in a patient population with a mean BMI greater than 50 kg/m^2.
h. Thoracic surgery: Because of the few trials of patients undergoing thoracic surgery, dosing recommendations are based on the evidence for pharmacologic agents in general surgery.
i. Coronary artery bypass surgery
   i. Because of the few trials of patients undergoing coronary artery bypass surgery, dosing recommendations are based on the evidence for pharmacologic agents in general surgery.
   ii. Because of concerns for the higher incidence of heparin-induced thrombocytopenia in patients undergoing cardiac surgery, LMWH may be preferred to LDUH for prophylaxis.

Table 14. VTE Prophylaxis in Non-orthopedic Surgery[a]

Surgical Indication	Unfractionated Heparin	Enoxaparin	Dalteparin	Fondaparinux
General surgery	5000 units SC q8hr or 5000 units SC q12hr	40 mg SC q24hr	5000 units SC q24hr	2.5 mg SC q24hr
Neurosurgery	5000 units SC q8hr	40 mg SC q24hr	Insufficient evidence	Insufficient evidence
Vascular surgery	5000 units SC q8hr or 5000 units SC q12hr	40 mg SC q24hr	5000 units SC q24hr	2.5 mg SC q24hr
Gynecologic	5000 units SC q8hr or 5000 units SC q12hr	40 mg SC q24hr	5000 units SC q24hr	2.5 mg SC q24hr
Urologic	5000 units SC q8hr or 5000 units SC q12hr	40 mg SC q24hr	5000 units SC q24hr	2.5 mg SC q24hr
Laparoscopic	Patients undergoing laparoscopic procedures with no additional VTE risk factors do not require prophylaxis beyond early ambulation			
Bariatric	5000 units SC q8hr	40 mg SC q12hr	7500 units SC q24hr	5 mg SC q24hr
Thoracic	5000 units SC q8hr or 5000 units SC q12hr	40 mg SC q24hr	5000 units SC q24hr	2.5 mg SC q24hr
Coronary artery bypass	5000 units SC q8hr or 5000 units SC q12hr	40 mg SC q24hr	5000 units SC q24hr	Not discussed in current guidelines

[a]See Box 6 for recommendations for dosing parenteral anticoagulants in special populations, including those with obesity.
q = every; SC = subcutaneous(ly); VTE = venous thromboembolism.

D. Hospitalized (Nonsurgical, Noncritically Ill) Medical Patients
   1. A heterogeneous group of hospitalized nonsurgical patients
   2. Risk of VTE is typically lower than in surgical patients, but medically ill patients make up around 60% of all VTE cases. Risk assessment models such as the Padua Prediction Score may be used to assess the VTE risk and, subsequently, the indication for pharmacologic prophylaxis in hospitalized nonsurgical medical patients. Table 15 shows a detailed Padua Prediction Score risk assessment model.
   3. Table 16 describes pharmacologic and/or mechanical prophylactic recommendations according to the 2012 American College of Chest Physicians guidelines.
   4. The ASH guidelines recommend LMWH or fondaparinux over LDUH or DOAC (e.g., low-dose rivaroxaban). Table 17 describes VTE prophylactic dosing for hospitalized (nonsurgical) patients.
   5. Guidelines recommend against pharmacologic prophylaxis beyond the period of patient immobilization or acute hospital stay.

Table 15. VTE Risk Assessment with Padua Prediction Score in Hospitalized Medical Patients

Risk Factors	Score
Active cancer[a]	3
Previous VTE[b]	3
Reduced mobility[c]	3
Known thrombophilic condition[d]	3
Recent (< 1 mo) trauma and/or surgery	2
Older age (≥ 70)	1
Cardiac and/or respiratory failure	1
Acute MI or ischemic stroke	1
Acute infection and/or rheumatologic disorder	1
Obesity (BMI ≥ 30 kg/m^2)	1
Active hormonal treatment	1

[a]Local or distant metastases and/or recipient of chemotherapy or radiotherapy within the past 6 mo.

[b]Excludes individuals with a history of superficial vein thrombosis.

[c]Anticipated bed rest for at least 3 days.

[d]Defects of antithrombin, protein C or protein S, factor V Leiden, G20210A prothrombin mutation, antiphospholipid syndrome.

BMI = body mass index; MI = myocardial infarction; VTE = venous thromboembolism.

Table 16. VTE Prophylaxis for Hospitalized (Nonsurgical, Noncritically Ill) Medical Patients

Padua Prediction Score	VTE Risk	Bleeding Risk	Recommendation
< 4	Low	—	No prophylaxis
≥ 4	High	Low	LDUH, LMWH, or fondaparinux Alternative: Low-dose rivaroxaban
		High[a]	Mechanical prophylaxis (GCS or IPC)

[a]Risk outweighs benefit in medically ill patients with an active bleed or at high risk of bleeding. The strongest risk factors are those with an odds ratio > 3 for bleeding and include active gastroduodenal ulcer, history of bleeding within 90 days, and Plt < 50,000/mm^3.

GCS = gradual compression stocking; IPC = intermittent pneumatic compression; LDUH = low-dose unfractionated heparin; LMWH = low-molecular-weight heparin; VTE = venous thromboembolism.

5. Practical issues
    a. In head-to-head trials of LDUH 5000 units subcutaneously every 8 hours and enoxaparin 40 mg subcutaneously daily, the regimens had similar efficacy, except for in medically ill patients (heart failure and ischemic stroke) at higher risk, in which enoxaparin may confer greater protection against VTE. In the same trials, enoxaparin had significantly less hematoma (greater than 5 cm) than LDUH. Although some data suggest a lower bleeding rate with LMWH in medically ill patients, these findings are not consistent across trials.
    b. Many clinical trials have not shown efficacy with LDUH 5000 units every 12 hours; therefore, LDUH 5000 units every 8 hours may be the preferred LDUH regimen.
    c. Enoxaparin 30 mg subcutaneously every 24 hours is recommended for patients with renal insufficiency (CrCl less than 30 mL/minute).
    d. Enoxaparin 20 mg once daily is equal in efficacy to LDUH 5000 units every 12 hours but was found to be no more effective than placebo.

Table 17. Venous Thromboembolism Prophylaxis in Hospitalized (Nonsurgical, Noncritically Ill) Patients

Low-Dose Unfractionated Heparin	Enoxaparin	Dalteparin	Fondaparinux[a]	Rivaroxaban
5000 units SC q8hr or 5000 units SC q12hr	40 mg SC daily	5000 units SC daily	2.5 mg SC daily	10 mg orally daily

[a]Not FDA approved.

q = every; SC = subcutaneous(ly).

6. Extended prophylaxis
    a. Risk of VTE extends beyond discharge, with almost two-thirds of all events occurring within 30 days after hospitalization.
    b. Extended prophylaxis (35–42 days) with enoxaparin has shown a significant reduction in developing VTE, but with significantly more major bleeding than enoxaparin for 10 days.
    c. Rivaroxaban is the only available DOAC with FDA approval for use in VTE prophylaxis. Rivaroxaban is approved for extended VTE prophylaxis (35 ± 4 days) in medically ill patients with moderate to severe restricted morbidity and at least one of the following additional risk factors: age 75 or older, prolonged immobilization, history of cancer, history of VTE, history of heart failure, thrombophilia, acute infectious disease contributing to hospitalization, or BMI greater than 35 kg/m^2.
        i. The MAGELLAN trial (n=8101) showed a significant reduction in VTE events with rivaroxaban 10 mg orally daily compared with enoxaparin 40 mg subcutaneously daily, but patients had significantly more major bleeding at day 35 (RR 0.65; 95% CI, 0.49–0.87; p=0.004).
        ii. A subpopulation analysis of MAGELLAN was conducted to reevaluate the risk-benefit profile. Five risk factors for major and fatal bleeding were identified and removed: treatment of active cancer during admission, use of dual antiplatelet therapy, history of bronchiectasis/pulmonary cavitation/pulmonary hemorrhage, active gastroduodenal ulcer in the previous 3 months, and active GI bleeding or any bleeding in the previous 3 months. These patients made up about 20% of the initial study population in the original MAGELLAN trial.
        iii. In the subpopulation (n=6447), VTE events were significantly reduced with rivaroxaban compared with enoxaparin/placebo (RR 0.68; 95% CI, 0.53–0.88), and major bleeding was not significantly increased (RR 1.48; 95% CI, 0.77–2.84).
        iv. Elimination of these five groups was prospectively studied in the MARINER trial, in which major bleeding was similar to placebo for extended VTE prophylaxis (HR 1.88; 95% CI, 0.84–4.23).

d. For those with moderate to severe immobility and other risk factors for VTE and not at high risk of bleeding, use of rivaroxaban for VTE prophylaxis can be considered for extended duration of use for 35 days (±4), which includes during hospital stay and after discharge.

E. Critically Ill Patients
   1. Patients at very high risk of developing VTE
   2. Typically includes patients in general critical care environments, including patients with trauma, acute spinal cord injury, and burns
   3. Critically ill patients should be offered VTE prophylaxis with LMWH or LDUH unless there is evidence of bleeding or patients are deemed at high risk of bleeding (Table 18).
   4. Recommend mechanical prophylaxis for patients with active bleeding or at high bleeding risk. Substitute LMWH or LDUH when bleeding risk decreases.
   5. The ASH guidelines recommend use of LMWH over LDUH.
   6. Practical issues
      a. Trauma
         i. A meta-analysis showed LDUH to be no more effective than control.
         ii. Enoxaparin 30 mg twice daily has better efficacy than LDUH 5000 units twice daily.
         iii. Observational analysis of 18,010 trauma patients showed a significant reduction in VTE events and death in patients receiving enoxaparin 30 mg twice daily compared with LDUH 5000 units three times daily.
         iv. Evidence for dalteparin is based on observational data.
         v. Pharmacologic prophylaxis can safely be initiated within 24–36 hours. Pharmacologic prophylaxis for patients with acute spinal cord injury may need to be delayed for 48–72 hours.
         vi. Patients with traumatic brain injury with a stable repeat head CT should receive pharmacologic prophylaxis within 72 hours after injury because systematic reviews have shown reduced VTE incidence without increased risk of intracranial hemorrhage.
         vii. Patients with severe trauma (e.g., injury severity score greater than 23) may present with antithrombin deficiency; therefore, subcutaneous prophylaxis may be insufficient. Although not prospectively evaluated, an option may be to use a heparin infusion while the patient is in the ICU early in therapy. Only a slight increase in the activated PTT (aPTT) (e.g., 35–45 seconds) would be targeted for VTE prevention.
      b. Acute spinal cord injury
         i. Use of LDUH three times daily had DVT and bleeding rates similar to enoxaparin twice daily, but PE was significantly reduced with enoxaparin.
         ii. Although enoxaparin 30 mg twice daily should be used during the acute injury period (about 2–3 weeks), either LDUH or LMWH can be used during the rehabilitation period.
         iii. In a retrospective case-control study, dalteparin 5000 units daily failed to show noninferiority to enoxaparin 30 mg twice daily in preventing VTE (9.7% vs. 1.6%). Further investigations of dalteparin are warranted.
      c. Burns – Current evidence in patients with burns is largely limited to observational studies with LDUH, enoxaparin, and dalteparin. The most commonly used regimen is LMWH with dosing adjusted according to anti-factor Xa (anti-Xa) concentrations or LDUH 5000 units subcutaneously every 12 hours.
      d. General critical care
         i. In medically ill or postoperative general surgery patients, LDUH or LMWH can be used. In orthopedic surgery or trauma, LMWH is preferred.
         ii. If mechanical prophylaxis is selected because of a patient's high risk of bleeding, the patient should be reevaluated often and changed to pharmacologic prophylaxis when the bleeding risk decreases.

iii. Some pharmacodynamic studies suggest that critical care patients with significant edema or critical care patients receiving vasopressors will not achieve detectable anti-Xa concentrations with LMWH.
iv. In the largest trial of VTE prevention in critical care patients, dalteparin 5000 units subcutaneously once daily provided similar protection against proximal DVT and better protection against PE, similar bleeding, and less heparin-induced thrombocytopenia than LDUH 5000 units twice daily.
v. Dalteparin does not have significant accumulation in critical care patients with renal insufficiency.
vi. A retrievable inferior vena cava filter may be considered for PE prophylaxis, but this practice has limited evidence and is controversial.

Table 18. Venous Thromboembolism Prophylaxis in Critically Ill Patients

Critical Care Setting	Low-Dose Unfractionated Heparin	Low-Molecular-Weight Heparin	Fondaparinux
Trauma	Insufficient evidence	Dalteparin 5000 units SC q24hr or enoxaparin 30 mg SC q12hr	Insufficient evidence
Acute spinal cord injury	5000 units SC q8hr	Enoxaparin 30 mg SC q12hr or Enoxaparin 40 mg SC q24hr	Insufficient evidence
Burns	5000 units SC q8hr or 5000 units SC q12hr	Dalteparin 5000 units SC q24hr or Enoxaparin 40 mg SC q24hr	Insufficient evidence
General critical care	5000 units SC q8hr or 5000 units SC q12hr	Dalteparin 5000 units SC q24hr or enoxaparin 30 mg SC q12hr or enoxaparin 40 mg SC q24hr	Insufficient evidence 2.5 mg SC daily may be an option in suspected HIT

HIT = heparin-induced thrombocytopenia; q = every; SC = subcutaneous(ly).

F. Duration of VTE Prophylaxis: Varies depending on patient risk and group (Table 19)

Table 19. Duration of VTE Prophylaxis

Indication	Duration
General medically ill patients	• Length of hospital stay or as long as immobile during acute illness • Rivaroxaban 31–39 days including inpatient and outpatient
Major general surgery	• Length of hospital stay
Major general surgery in patients with previous VTE	• Beyond hospital discharge for up to 28 days
Surgery for GI, GU, or gynecologic cancer	• Beyond hospital discharge for up to 28 days
Major orthopedic surgery (e.g., THA, TKA, HFS)	• At least 10–14 days; extending to outpatient period for a total of up to 35 days is suggested
Critical care patients	• For the duration of the ICU stay with reevaluation when the patient is transferred to the general medical ward
Major trauma	• Until hospital discharge and continued prophylaxis in patients with impaired mobility who undergo inpatient rehabilitation (up to 8 wk)
Patients with spinal cord injury	• Until hospital discharge in patients with incomplete injuries • For 8 wk in patients with uncomplicated complete motor injury • For 12 wk or until discharge from rehabilitation in patients with complete motor injury and other risk factors

GI = gastrointestinal; GU = genitourinary; HFS = hip fracture surgery; THA = total hip arthroplasty; TKA = total knee arthroplasty; VTE = venous thromboembolism.

Patient Case

7. B.G. is a 62-year-old male (height 175 cm, weight 110 kg) hospitalized for a heart failure exacerbation. He has symptoms when doing only limited exertion and has been out of bed only to use the bathroom for the past 3 days. His medical history also includes stable ischemic heart disease, hypertension, type 2 diabetes, and a PE 2 years ago. He smokes 2 packs of cigarettes/day and drinks 1 glass of wine with dinner most evenings. His medications include bisoprolol 5 mg orally daily, lisinopril 10 mg orally daily, aspirin 81 mg orally daily, ranolazine 1000 mg orally twice daily, furosemide 40 mg orally daily, spironolactone 25 mg orally daily, and metformin 1000 mg orally twice daily. His blood pressure today is 110/70 mm Hg and heart rate is 58 beats/minute. His laboratory values are normal except for a BNP of 1498 ng/mL. Which is the most appropriate VTE prevention strategy for B.G.?

   A. Administer fondaparinux 5 mg subcutaneously daily.

   B. Administer apixaban 2.5 mg orally twice daily.

   C. Administer enoxaparin 40 mg subcutaneously daily.

   D. His risk does not warrant prophylactic therapy.

G. Special Populations – Box 6 provides information on use of VTE prophylaxis in special populations.

Box 6. Use of Venous Thromboembolism Prophylaxis in Special Populations

Severe Renal Insufficiency

- Patients with renal insufficiency are at higher risk of bleeding, regardless of the anticoagulant used
- Patients with SCr > 2.5 mg/dL have been excluded from most clinical trials
- Enoxaparin should be dosed at 30 mg subcutaneously once daily, regardless of the indication for CrCl < 30 mL/min
- Dalteparin does not seem to significantly accumulate in patients with severe renal insufficiency until the CrCl is < 20 mL/min when prophylactic doses are used
- Fondaparinux is contraindicated in patients with a CrCl < 30 mL/min and rivaroxaban in patients with a CrCl < 15 mL/min
- Patients receiving hemodialysis (renal failure) should receive subcutaneous LDUH

Obesity

- American College of Chest Physicians guidelines recommend possible weight-adjusted dosing in patients with obesity but provide no insight regarding at what weight this should be considered or what the "adjusted" dosing should be. Patients with obesity are at considerable risk of PE, but data from clinical trials on drug dosing are limited
- Studies suggest that the typical LMWH prophylactic dose results in less anticoagulant effect, but clinical outcomes data are lacking
- Enoxaparin 40 mg subcutaneously twice daily has been more efficacious than 30 mg subcutaneously twice daily in patients undergoing bariatric surgery
- It is reasonable to use enoxaparin 40 mg subcutaneously twice daily, enoxaparin 0.5 mg/kg subcutaneously twice daily, dalteparin 7500 units once daily, fondaparinux 5 mg once daily, or LDUH 7500 units three times daily in patients with a BMI > 40 kg/m^2 or weight > 120 kg
- Injections of enoxaparin into the thigh in patients with obesity have a lower bioavailability than injections into the abdomen

Box 6. Use of Venous Thromboembolism Prophylaxis in Special Populations (*Cont'd*)

Pregnancy

- Warfarin has been associated with congenital abnormalities when used during the first trimester and is therefore contraindicated. Although warfarin could be used during the second trimester, it is typically avoided throughout pregnancy
- LMWH or LDUH can be used throughout pregnancy
- DOACs currently have no role in pregnancy

CrCl = creatinine clearance; DOAC = direct oral anticoagulant; LDUH = low-dose unfractionated heparin; LMWH = low-molecular-weight heparin; PE = pulmonary embolism.

IV. TREATMENT OF VENOUS THROMBOEMBOLISM

A. Introduction
   1. Around 2 million symptomatic and asymptomatic cases of VTE occur in the United States each year, with 25% having sudden death as the initial PE symptom.
      a. Around 600,000 cases of PE each year
      b. More than 60,000–100,000 deaths from VTE each year in the United States
   2. Consequences of VTE
      a. 33% will develop a recurrent VTE event within 10 years.
      b. 30%–50% of patients develop postthrombotic syndrome (swelling, pain, discoloration, and scaling).
      c. After a DVT event, 20% of patients die within the following year.
      d. After a PE event, 40% of patients die within the following year.

B. Pathophysiology
   1. Venous thrombosis forms from the components of the Virchow triad: venous stasis, vascular injury, and/or an inherited or acquired hypercoagulable state.
   2. Components of the Virchow triad are broken down into a list of risk factors (see Box 5). Risk factors are cumulative, and some carry a higher risk than others (e.g., previous VTE, cancer, orthopedic surgery).
   3. Thrombus typically begins in the cusps of venous valves, where blood is more static. Vascular injury because of trauma or hypoxia initiates the clotting cascade with interaction between endothelial tissue factor and factor VII.
   4. An embolism from a DVT will lodge itself in the next available capillary bed, which is in the pulmonary vasculature, leading to PE.
   5. Thrombosis often forms in and around venous valves, causing them to curl. Despite therapy, these valves may not recover their initial shape and function, which leads to continued venous stasis and continued risk of recurrent DVT and postthrombotic syndrome.
   6. Most upper extremity DVTs are related to the use of central venous catheters.

C. Clinical Presentation and Assessment
   1. Deep Vein Thrombosis
      a. Although many cases are asymptomatic, these acute asymptomatic DVTs can still have long-term complications.
      b. Most thrombi begin in the lower extremities.
      c. Superficial vein thrombosis typically does not embolize unless it extends into a deep vein, is at least 5 cm long, or is within 10 cm of the saphenofemoral junction.
      d. Proximal DVTs are more likely to embolize than isolated calf DVTs.

e. Signs and symptoms are nonspecific (Box 7) and need to be confirmed with the appropriate diagnostic test.
   i. The Wells model can be used to determine the patient's pretest probability of developing a DVT and guide further diagnostic testing (Table 20).
   ii. Patients with low (3%) or moderate (17%) pretest probability, defined by a Wells score of 0 and 1–2, respectively, should continue assessment with D-dimer interpretation. If D-dimer is elevated (greater than 500 ng/mL for most assays), the patient should continue to diagnostic imaging.
   iii. D-dimer is a breakdown product of fibrin and fibrinogen and is typically elevated in the setting of VTE. Although D-dimer is sensitive for clot formation, it is nonspecific and can also be elevated from conditions such as inflammation and infection. Therefore, a positive test does not confer a definitive VTE diagnosis, but aids in ruling out thrombosis.
   iv. Patients with a high pretest probability (75%) , defined by a Wells score of 3 or greater, should continue to duplex ultrasonography or other imaging studies to confirm diagnosis.
   v. Venography is the gold standard diagnostic tool, but it is invasive (injecting dye into a vein in the heel/ankle), may be painful, and is rarely used in clinical practice.
   vi. Duplex ultrasonography is most commonly used in clinical practice for diagnosing DVT. It is noninvasive and inexpensive and has higher specificity and sensitivity than older versions of Doppler ultrasonography.

Box 7. Clinical Presentation of Deep Vein Thrombosis and Pulmonary Embolism

Deep Vein Thrombosis
(+) Homan sign (pain in back of knee with dorsiflexion of the foot)
Leg pain
Calf tenderness
Swelling
Skin discoloration (redness)
Leg warmth
Pulmonary Embolism
Tachycardia
Tachypnea
Palpitation
Dyspnea
Cough/hemoptysis
Chest pain

Table 20. Wells Clinical Model for Evaluating the Pretest Probability of DVT[a]

Clinical Characteristics	Score
Active cancer (cancer treatment within previous 6 mo or currently receiving palliative treatment)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recent bed confinement for ≥ 3 days or major surgery within previous 12 wk requiring general or regional anesthesia	1
Localized tenderness along distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling at least 3 cm larger than that on the asymptomatic side (measured 10 cm below tibial tuberosity)	1
Pitting edema confined to the symptomatic leg	1
Collateral superficial veins (non-varicose)	1
Previously documented DVT	1
Alternative diagnosis at least as likely as DVT	-2

[a]Clinical probability of DVT: low = 0; moderate = 1 or 2; high ≥ 3. In patients with symptoms in both legs, the more symptomatic leg is used.
DVT = deep vein thrombosis.

2. Pulmonary embolism
    a. PE is classified as massive (hemodynamic instability including systolic blood pressure less than 90 mm Hg and cardiogenic shock), submassive (normal systolic blood pressure, right ventricular dysfunction, and positive biomarkers [e.g., elevated troponin]), and nonmassive (hemodynamic stability). Similar to DVT cases, many PE cases are asymptomatic. More than 90% of thrombi begin in the lower extremities and embolize.
    b. Signs and symptoms are nonspecific (see Box 7) and require confirmation with the appropriate diagnostic test.
        i. The Wells model can be used to determine the pretest probability of a patient developing a PE (Table 21).
        ii. Patients who have a low (3%–10%) or moderate (15%–35%) pretest probability, defined by a Wells score of 0–1 and 2–6, respectively, should continue assessment with D-dimer. If D-dimer is elevated, the patient should continue to diagnostic imaging.
        iii. D-dimer is similar to use with DVT. Serum concentrations are typically elevated in patients with PE.
        iv. Patients deemed at high risk (35%–70%), defined by a Wells score of 7 or greater, should continue with CT or other imaging studies to confirm the diagnosis of PE.
        v. CT pulmonary angiography (CTPA) with radiographic contrast is the most common (and preferred) test used to diagnose PE. Positive results have good specificity and generally confirm the diagnosis. Both the sensitivity and the specificity of the test are improved with central emboli over those that are more peripheral.
        vi. Ventilation/perfusion (V/Q) scan may be used if CTPA is unavailable if the patient has renal insufficiency and/or hypersensitivity to contrast dye. V/Q scan measures the distribution of blood flow and airflow in the lungs. A "mismatch" between blood flow and airflow in one area confers a high probability of PE. Specificity can be impaired in patients with heart failure, chronic obstructive pulmonary disease, or asthma. A scan with a negative finding has good specificity and generally rules out the diagnosis of PE.

Table 21. Wells Criteria Clinical Model for Evaluating the Pretest Probability of PE[a]

Clinical Characteristic	Score
Cancer	1
Hemoptysis	1
Previous PE or DVT	1.5
Heart rate > 100 beats/min	1.5
Recent surgery or immobilization	1.5
Clinical signs of DVT	3
Alternative diagnosis less likely than PE	3

[a]Clinical probability of PE: low 0–1; moderate 2–6; high ≥ 7.

DVT = deep vein thrombosis; PE = pulmonary embolism.

D. Acute Treatment of VTE
   1. Three approaches to VTE treatment (Table 22)
   2. The 2021 American College of Chest Physicians guidelines prefer DOACs to warfarin for patients with VTE without cancer because of reduced bleeding risk and greater convenience for patients and health care providers.
   3. The 2020 ASH guidelines also prefer DOACs to warfarin for the treatment of VTE.

Table 22. Approaches to VTE Treatment

Treatment Strategy	Anticoagulant Choices
Bridging therapy	Injectable anticoagulant (UFH, LMWH, or fondaparinux) initiated with warfarin and overlapped for at least 5 days and until the INR is ≥ 2.0. Then discontinue injectable anticoagulant and continue warfarin dose-adjusted to INR target of 2.5 (±0.5) for indicated duration
Switching therapy	Injectable anticoagulant (UFH, LMWH, or fondaparinux) for first 5 days; then discontinue injectable anticoagulant therapy and initiate dabigatran or edoxaban for the indicated duration
Monotherapy	Initiate rivaroxaban or apixaban at higher initial dose and then convert patient to lower maintenance dose for the indicated duration

LMWH = low-molecular-weight heparin; UFH = unfractionated heparin.

   4. Bridging therapy approach to VTE treatment
      a. Because of the delay in achieving systemic anticoagulation with warfarin therapy and the significant thrombus burden in patients with VTE, an injectable anticoagulant is initiated on the suggestion of a VTE and bridged to warfarin if the diagnosis is confirmed.
      b. Table 23 shows dosing of injectable anticoagulants for VTE treatment. Achieving therapeutic anticoagulation within the first 24 hours has been associated with reduced rates of recurrent VTE events.
      c. If using the bridging therapy approach, the American College of Chest Physicians guidelines recommend initial injectable anticoagulant therapy with an LMWH or fondaparinux over intravenous or subcutaneous UFH. Weight-adjusted dosing should be based on actual body weight.
      d. Warfarin dosing in the stable outpatient setting is similar to that discussed in the AF section, including a target INR of 2.5 (±0.5). In acute situations, dosing may depend on cofactors that drive initial dosing approaches.

e. Bridging to warfarin would likely be the preferred approach in the following:
   i. When patients have renal dysfunction because patients in the DOAC trials were excluded if their CrCl was less than 30 mL/minute (less than 25 mL/minute for apixaban)
   ii. When patients cannot afford DOAC therapy
   iii. When the transition to outpatient therapy makes acquiring a DOAC difficult. Pharmacists play a crucial role in helping to confirm insurance coverage and other transition-of-care issues in these patients.

Table 23. Dosing of Injectable Anticoagulants for VTE Treatment

Agent and Route	Dosing
Unfractionated Heparin (IV)	
IV UFH[a]	Weight adjusted with an initial bolus of 80 units/kg (max initial bolus of 10,000 units), followed by an initial infusion of 18 units/kg/hr (max initial infusion of 2000 units/hr). Subsequent doses should be adjusted to maintain the institution's goal aPTT
Low-Molecular-Weight Heparin (SC)	
Enoxaparin	1 mg/kg q12hr or 1.5 mg/kg q24hr[b]; if CrCl < 30 mL/min, administer 1 mg/kg q24hr
Dalteparin[c,d]	100 units/kg q12hr or 200 units/kg q24hr; CrCl < 30 mL/min – Contraindicated
Pentasaccharide (SC)	
Fondaparinux	Weight < 50 kg – Administer 5 mg q24hr Weight 50–100 kg – Administer 7.5 mg q24hr Weight > 100 kg – Administer 10 mg q24hr CrCl < 30 mL/min – Contraindicated

[a]IV administration is preferred because of improved dosing precision.

[b]1.5 mg/kg q24hr should be avoided in patients with current or history of malignancy, weight > 120 kg, deep vein thrombosis with iliac vein involvement, or antiphospholipid syndrome.

[c]Not FDA approved for VTE treatment in patients without cancer, which may create insurance coverage issues.

[d]Dosing for VTE in patients with active cancer includes 200 units/kg SC q24hr for 30 days, then 150 units/kg SC q24hr thereafter.

aPTT = activated partial thromboplastin time; CrCl = creatinine clearance; IV = intravenous(ly); q = every; SC = subcutaneous(ly); UFH = unfractionated heparin; VTE = venous thromboembolism.

5. Switching therapy approach in VTE treatment
   a. Dabigatran was evaluated in the RE-COVER I (n=2539) and II (n=2568) trials. The trials had the same design, and both enrolled patients with DVT (67%–69%), PE (21%–23%), or both (9%–10%).
      i. All patients received a median of 9 days of injectable anticoagulation. Patients randomized to dabigatran 150 mg orally twice daily started the drug after discontinuing the injectable anticoagulant (Table 24). Patients randomized to dose-adjusted warfarin started the drug at the same time as the injectable anticoagulant and were bridged to an INR of 2.0–3.0 for at least 5 days. Patients were treated for 6 months. TTR in the warfarin group was 59.9% in RE-COVER I and 56.9% in RE-COVER II.
      ii. In the combined trials (n=5107), the primary end points of symptomatic VTE events were similar between dabigatran and warfarin (2.4% vs. 2.2%; p=NS). Noninferiority was achieved (p<0.001).
      iii. Major bleeding was not significantly reduced with dabigatran (1.4% vs. 2.0%; HR 0.73; 95% CI, 0.48–1.11).
      iv. Major and clinically relevant nonmajor (CRNM) bleeding combined were significantly reduced with dabigatran compared with warfarin 5% vs. 8.5% (HR 0.62; 95% CI, 0.50–0.76).

b. Edoxaban was evaluated in the Hokusai-VTE trial (n=8240), which included patients with DVT (60%), PE (30%), or both (10%).
   i. All patients received a median of 7 days of injectable anticoagulant. Patients randomized to edoxaban 60 mg orally daily (or 30 mg orally daily based on body weight [60 kg or less] or moderate renal insufficiency [CrCl 30–50 mL/minute] or in patients who received potent P-gp inhibitors concomitantly) started the drug after discontinuing the injectable. Patients randomized to dose-adjusted warfarin started the drug at the same time as the injectable anticoagulant and were bridged to an INR of 2.0–3.0 for at least 5 days. Patients were followed for 12 months. The reduced edoxaban dose was used in 18% of patients with maintained efficacy and safety. TTR in the warfarin group was 63.5%.
   ii. The primary end point of symptomatic VTE events was similar between edoxaban and warfarin (3.2% vs. 3.5%; p=NS). Noninferiority was achieved (p<0.001).
   iii. The patient subgroup enrolled with severe PE, defined as producing right ventricular dysfunction (n=938), had a significant 48% reduction in the primary end point compared with warfarin (3.3% vs. 6.2%, HR 0.52; 95% CI, 0.28–0.98).
   iv. Major bleeding was not significantly reduced with edoxaban (1.4% vs. 1.6%) overall.
   v. Major and CRNM bleeding combined was significantly reduced with edoxaban compared with warfarin (8.5% vs. 10.3%).

6. Monotherapy approach in VTE treatment
   a. Rivaroxaban was evaluated in the EINSTEIN DVT (n=3449) and EINSTEIN PE (n=4832) trials. Although the trial designs were the same, they included different patient populations.
      i. Rivaroxaban 15 mg orally twice daily for 21 days, followed by 20 mg orally daily thereafter was initiated and compared with enoxaparin 1 mg/kg subcutaneously every 12 hours bridged to dose-adjusted warfarin therapy (INR 2.0–3.0). TTR in the warfarin group was 57.7% in EINSTEIN DVT and 62.7% in EINSTEIN PE. Median duration of injectable anticoagulant was 8 days. Investigators determined whether patients would be treated for 3, 6, or 12 months. Only 12% and 5% of patients were treated for 3 months in the EINSTEIN DVT and PE trials, respectively.
      ii. Many patients in the rivaroxaban arms of EINSTEIN DVT (73%) and EINSTEIN PE (93%) still received injectable anticoagulation before enrolling in the study. These patients were transitioned to rivaroxaban upon entering the trial. Efficacy and safety outcomes did not differ regardless of whether patients received initial doses of injectable anticoagulation before receiving rivaroxaban.
      iii. In the combined trials (n=8282), the primary end point of symptomatic VTE events was similar between rivaroxaban and standard care (2.1% vs. 2.3%; p=0.41). Noninferiority was achieved (p<0.001).
      iv. Major bleeding was reduced by a relative 46% with rivaroxaban compared with standard care (1% vs. 1.7%; p=0.002), whereas CRNM bleeding did not differ (8.6% vs. 8.4%).
      v. Patients with fragility (age older than 75, CrCl less than 50 mL/minute, or weight less than 50 kg) had a greater than 70% significant relative reduction in major bleeding, with each component of fragility reaching statistical significance independently.
   b. Apixaban was evaluated in the AMPLIFY (n=5395) trial, which included patients with DVT (65%), PE (25%), or both (9%).
      i. Apixaban 10 mg orally twice daily for 7 days, followed by 5 mg orally twice daily thereafter was initiated and compared with enoxaparin 1 mg/kg subcutaneously every 12 hours bridged to dose-adjusted warfarin therapy (INR 2.0–3.0). Median duration of injectable anticoagulant was 6.5 days, and TTR in those randomized to warfarin was 61%. Patients were treated for 6 months.

ii. 86% of patients in the apixaban arm initially received at least one dose of injectable anticoagulant before entering the study. These patients were transitioned to apixaban upon entering the trial. Efficacy and safety outcomes did not differ regardless of whether patients received initial doses of injectable anticoagulation before receiving apixaban.
iii. The primary end point of symptomatic VTE events was similar between apixaban and standard care (2.3% vs. 2.7%; p=NS). Noninferiority was achieved (p<0.001).
iv. Major bleeding was reduced by a relative 70% with apixaban compared with standard care (0.6% vs. 1.8%; p<0.001).
v. CRNM bleeding was also reduced with apixaban (3.8% vs. 8.0%; p<0.001).

Table 24. DOAC Dosing in VTE

Agent	Standard Dosing	Dose Adjustment[a]	Avoid Use[a]
Dabigatran	150 mg PO BID after 5–10 days of injectable anticoagulation	None	• CrCl ≤ 30 mL/min • Avoid use with CrCl 30–50 mL/min and concomitant use of P-gp inhibitors • P-gp inducers (e.g., rifampin) • Chemotherapy agents – Vinblastine, doxorubicin, imatinib, crizotinib, vandetanib, sunitinib, abiraterone, and enzalutamide
Rivaroxaban	15 mg PO BID with food for 21 days, followed by 20 mg PO daily with food. After 6 mo, dose can be reduced to 10 mg daily for extended-phase treatment. The 10-mg dose need not be administered with food	None	• CrCl ≤ 30 mL/min • Strong CYP3A4 and P-gp inducers[b] • Moderate-severe hepatic impairment (Child-Pugh class B or C) • Strong CYP3A4 and P-gp inhibitors[c] • Chemotherapy agents – Vinblastine, doxorubicin, imatinib, crizotinib, vandetanib, sunitinib, abiraterone, and enzalutamide
Apixaban	10 mg PO BID for 7 days, followed by 5 mg PO BID. After 6 mo, dose can be reduced to 2.5 mg PO BID for extended-phase treatment	50% dose reduction if receiving 5 or 10 mg PO BID with strong CYP3A4 and P-gp inhibitors (e.g., protease inhibitors, itraconazole, ketoconazole, conivaptan)	• Severe hepatic impairment (Child-Pugh class C) • Strong CYP3A4 and P-gp inducers[b] • If receiving 2.5 mg BID – Strong CYP3A4 and P-gp inhibitors[c] • Chemotherapy agents – Vinblastine, doxorubicin, imatinib, crizotinib, vandetanib, sunitinib, abiraterone, and enzalutamide
Edoxaban[d]	60 mg PO once daily after 5–10 days of injectable anticoagulation	30 mg once daily • CrCl 15–50 mL/min • Potent P-gp inhibitor (verapamil, dronedarone, or quinidine) • Weight ≤ 60 kg	• CrCl < 15 mL/min • P-gp inducers (e.g., rifampin) • Chemotherapy agents – Vinblastine, doxorubicin, imatinib, crizotinib, vandetanib, sunitinib, abiraterone, and enzalutamide

[a]CrCl in the DOAC trials was calculated using the Cockcroft-Gault equation with total body weight.

[b]Strong CYP3A4 and P-gp inducers include rifampin, phenytoin, carbamazepine, and St. John's wort.

[c]Strong CYP3A4 and P-gp inhibitors include protease inhibitors, itraconazole, ketoconazole, and conivaptan.

[d]Efficacy data are lacking with edoxaban for VTE treatment in patients with a CrCl > 95 mL/min.

BID = twice daily; CrCl = creatinine clearance; DOAC = direct oral anticoagulant; P-gp = P-glycoprotein; PO = oral(ly); VTE = venous thromboembolism.

7. Outpatient therapy
    a. Around 80% of patients with a DVT can be treated on an outpatient basis.
    b. Most patients with low-risk PE (defined as a patient clinically stable with good cardiopulmonary reserve; no contraindication such as recent bleeding, severe renal or liver disease, or severe thrombocytopenia; expected to be adherent to treatment; patient feels well enough to be treated at home) can also be treated at home. The ability to use a DOAC without injectable anticoagulation offers an attractive option and easier transition of care. Rivaroxaban was shown to be safe and effective using this approach in a small trial (HoT-PE) and significantly reduced resource use (MERCURY PE). Data with other DOACs are still developing.
    c. The 2021 American College of Chest Physicians guidelines recommend outpatient treatment of low-risk PE.

E. Secondary Prevention of VTE
1. All patients with VTE should be treated for at least 3 months (Table 25).
2. Patients without a transient or reversible cause should be considered for long-term, potentially indefinite, oral anticoagulant therapy. Data analyses consistently show significant reductions in VTE with continued therapy for 12–24 additional months. Once therapy is discontinued, VTE rates approach those of patients who did not receive extended therapy.
3. American College of Chest Physicians guidelines state that the oral anticoagulant need not be changed if therapy is continued beyond 3 months.
4. Options
    a. Adjusted-dose warfarin to an INR of 2.5 (±0.5)
    b. Dabigatran 150 mg twice daily has been noninferior to warfarin for efficacy, with similar major bleeding but less major and CRNM bleeding (RE-MEDY trial). Dabigatran was superior to placebo for efficacy, with similar major bleeding but more major and CRNM bleeding (RE-SONATE trial).
    c. Rivaroxaban 20 mg daily was superior to placebo for efficacy, with similar major bleeding and more major and CRNM bleeding (EINSTEIN-Extension trial). Both rivaroxaban 20 mg and rivaroxaban 10 mg once daily were superior to aspirin, with similar safety (EINSTEIN CHOICE) in patients who had already completed 6 months of therapy (see Table 25).
    d. Apixaban 5 mg and 2.5 mg twice daily were superior to placebo for efficacy, with similar safety (AMPLIFY-Extension) in patients who had already completed 6 months of therapy (see Table 25).
    e. No long-term trials of edoxaban have been completed beyond the Hokusai-VTE trial.
    f. Aspirin (100 mg daily) had a 32% relative reduction in recurrent VTE events compared with placebo in two trials after patients completed at least 6 months of oral anticoagulant therapy. Relative reductions in patients receiving a DOAC compared with placebo are typically 70%–80%. The only trial comparing a DOAC with aspirin was the EINSTEIN CHOICE, in which both rivaroxaban doses were superior to aspirin for efficacy, with similar low rates of bleeding.

Table 25. Duration of Anticoagulation Therapy in Patients with VTE

Indication	Therapy Duration	Comments
Provoked VTE[a]	3 mo	Recommendation applies to both proximal DVT and PE
First unprovoked VTE or provoked by persistent risk factor	At least 3 mo; then reassess for extended-phase anticoagulation	Continue oral anticoagulant therapy if patient is not at high risk of bleeding and is adherent to therapy Risk-benefit of indefinite therapy should be reassessed at least annually Preference for extended-phase anticoagulation with low-dose apixaban (2.5 mg twice daily) or rivaroxaban (10 mg once daily) over aspirin If discontinuing anticoagulant therapy, aspirin therapy is suggested to prevent recurrent VTE
First episode of VTE with inherited or acquired thrombophilia[b]	At least 3 mo; then reassess for extended-phase anticoagulation	Continue oral anticoagulant therapy if patient is not at high risk of bleeding and is adherent to therapy Dose-adjusted warfarin to INR target of 2.5 (±0.5) is preferred to other anticoagulants in patients with antiphospholipid syndrome Risk-benefit of indefinite therapy should be reassessed at least annually
First episode of cancer-associated VTE	At least 3–6 mo and consider extended duration as long as active cancer or for duration of cancer treatment	Apixaban, edoxaban, rivaroxaban, or LMWH is recommended over other anticoagulants LMWH is preferred to factor Xa inhibitors in patients with luminal GI malignancies
Second VTE (provoked or unprovoked)	Indefinite	Applies to patient not at high risk of bleeding

[a]Provoked VTE = transient or reversible risk factors including surgery, hospitalization, plaster cast immobilization within 3 mo, estrogen, pregnancy, prolonged travel (> 8 hr), lesser leg injuries, or immobilization within 6 wk.

[b]Factor V Leiden; prothrombin G20210A; antiphospholipid syndrome; excess factor VIII; deficiency in protein C or protein S; antithrombin deficiency.

DVT = deep vein thrombosis; INR = international normalized ratio; LMWH = low-molecular-weight heparin; PE = pulmonary embolism; VTE = venous thromboembolism.

F. Treatment of Cancer-Associated VTE
   1. Cancer is a significant risk factor for developing thrombosis.
      a. 15% of patients with cancer develop venous or arterial thrombosis.
      b. Cancer increases the risk of initial VTE by 4- to 9-fold.
      c. Chemotherapy can increase the risk by up to 6.5-fold.
      d. VTE is the second leading cause of death in most cancers.
      e. Risk of VTE varies depending on cancer type and patient- and treatment-related factors.
   2. Historically, LMWH has been the preferred anticoagulant in the treatment of cancer-associated VTE because it has shown improved efficacy compared with warfarin without an increased risk of bleeding.
   3. With growing evidence related to the efficacy and safety of DOACs in this patient population, the International Society on Thrombosis and Haemostasis (ISTH), American College of Chest Physicians, American Society of Clinical Oncology (ASCO), and National Comprehensive Cancer Network (NCCN) have provided recommendations for use. Table 26 presents guideline recommendations for parenteral or oral anticoagulants.

Table 26. Clinical Guideline Recommendations for Treatment of Cancer-Associated VTE

Clinical Guidelines	Recommendations
ISTH (2018)	• Low risk of bleeding: Rivaroxaban or edoxaban preferred (LMWH acceptable alternative) • High risk of bleeding[a]: LMWH preferred (rivaroxaban or edoxaban acceptable alternatives)
ASCO (2023)	• Initial treatment (5–10 days): LMWH, UFH, fondaparinux, apixaban, or rivaroxaban (LMWH preferred to UFH if parenteral anticoagulant initiated) • Long-term treatment (6 mo): LMWH, edoxaban, apixaban, or rivaroxaban preferred to VKA
American College of Chest Physicians (2021)	• General strategy: Factor Xa inhibitor preferred to LMWH ◦ Presence of luminal GI malignancy: LMWH or apixaban preferred to edoxaban or rivaroxaban
NCCN (2023)	• Patients without gastric or gastroesophageal lesions: DOACs (apixaban, edoxaban, rivaroxaban) preferred • Patients with gastric or gastroesophageal lesions: LMWH preferred (dalteparin > enoxaparin)

[a]High risk of bleeding considered luminal GI cancers, genitourinary or bladder cancers, active abnormalities of GI mucosal (e.g., duodenal ulcers, gastritis, esophagitis, or colitis).

DOAC = direct oral anticoagulant; GI = gastrointestinal; LMWH = low-molecular-weight heparin; UFH = unfractionated heparin; VKA = vitamin K antagonist.

4. Landmark trials for DOACs used in cancer-associated VTE:
    a. Factor Xa inhibitors
        i. Edoxaban (Hokusai-VTE Cancer trial) and rivaroxaban (SELECT-D) have been compared with dalteparin in studies of patients with cancer-induced thrombosis. Collectively, these DOACs showed reduced recurrent VTE, but with an increased incidence of major bleeding. Most of the excess bleeding occurred in patients with upper GI cancers.
        ii. Apixaban (ADAM-VTE and CARAVAGGIO) provided efficacy similar to dalteparin with similar major bleeding. The similar major bleeding in the overall trial results may have been due to lower enrollment of patients with upper GI cancers.
    b. Direct thrombin inhibitor
        i. Data are limited with the use of dabigatran in cancer-associated thrombosis, especially compared with LMWH. A trial that compared dabigatran with VKA showed similar efficacy and incidence of bleeding.
        ii. Guidelines do not currently recommend routine use of dabigatran in cancer-associated thrombosis.

Patient Case

8. A 48-year-old male (height 178 cm, weight 90 kg) presents to the ED with pain and swelling in his left leg. On examination, his leg is warm to the touch and tender and has 3+ pitting edema below the knee. His D-dimer is positive, and his duplex ultrasonography identifies a femoral-popliteal DVT. He understands that he will need to receive anticoagulant therapy but wants to avoid any injections, if possible. He has good insurance coverage. His other medical conditions are hypertension, HIV, and dyslipidemia. His medications include benazepril 20 mg orally daily, ritonavir 100 mg orally daily, darunavir 800 mg orally daily, emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg orally daily, and atorvastatin 10 mg orally daily. His vital signs are stable, and his CrCl is 78 mL/minute. Which is the most appropriate anticoagulant regimen to initiate for this patient?

   A. Rivaroxaban 15 mg orally twice daily for 21 days, followed by 20 mg orally daily.

   B. Edoxaban 60 mg orally daily.

   C. Warfarin 2.5 mg orally daily.

   D. Apixaban 5 mg orally twice daily for 7 days, followed by 2.5 mg orally twice daily.

V. REVERSAL OF ANTICOAGULATION

A. Blood Products
   1. In the reversal of anticoagulant therapy, blood products are often part of the management of major bleeding.
   2. Whole blood is spun into red cells and platelet-rich plasma. The platelet-rich plasma is spun again to create platelets and plasma, and the plasma is frozen (FFP).
   3. Packed RBCs (PRBCs)
      a. Not used for reversal but for management of bleeding to provide oxygen delivery to tissues.
      b. 1 unit (around 250 mL) has an Hct of 70%–80% (twice whole blood) and can increase a patient's Hgb by 1–2 g/dL.
      c. Risks include transfusion reactions (e.g., chills, fever, urticaria, tachycardia), infection, and transfusion-related lung injury.
   4. Platelets
      a. May be used for reversal of antiplatelet therapy, but data are inconsistent
      b. Each unit (200–300 mL) contains 300,000–600,000 platelets/mm^3.
      c. Same risk as with PRBCs
      d. Commonly part of a massive transfusion protocol
   5. Fresh frozen plasma (FFP)
      a. Cells have been spun out of blood, and the plasma contains the proteins in blood, mainly clotting factors.
      b. Must be frozen within 8 hours of blood collection and viable for 12 months
      c. Commonly underdosed for reversing warfarin therapy – Takes several units (around 4 units)
         i. Typical dose is 15–20 mL/kg (around 1.2–1.6 L).
         ii. Critically ill patients: 30 mL/kg (around 2.4 L)
      d. Requires type-and-crossing
      e. Takes 30–45 minutes to thaw
      f. Risks similar to those with PRBCs and platelets

6. Prothrombin complex concentrate (PCC)
    a. Clotting factor proteins are taken from a plasma sample.
    b. About 25-fold more concentrated in clotting factors than FFP
    c. Types (what each contains)
        i. 3-factor: Clotting factors II, IX, and X
        ii. 4-factor: Clotting factors II, VII, IX, and X (4PCC)
        iii. Activated PCC (aPCC): II, VIIa, IX, and X
        iv. All contain varying concentrations of protein C, protein S, and UFH (exception – aPCC does not contain UFH).
    d. Undergoes viral inactivation, reduces adverse effects, has a smaller volume than FFP, and does not require type-and-crossing
7. Cryoprecipitate
    a. Derived by thawing 1 unit of FFP in cold conditions (cryoprecipitate) (4°C) and then collecting the precipitated globulins, which are then resuspended in 20–40 mL of plasma
    b. Contains concentrations of factor VIII, XIII, von Willebrand factor, fibronectin, and fibrinogen
    c. May be used for bleeding from fibrinolytics to provide more fibrinogen to the patient. May be part of a massive transfusion protocol
    d. Dosing of cryoprecipitate can be calculated using the following formula: To increase serum fibrinogen 1 g/dL, administer cryoprecipitate 0.2 units × weight (in kg).
    e. Takes 10–20 minutes to thaw
    f. Fibrinogen concentrate (human) is also available.
8. Recombinant activated factor VII
    a. Not technically a blood product because of synthesis through recombinant technology
    b. Has been used to treat bleeding in patients receiving UFH, LMWH, and DOACs. Most trials are small and observational.
    c. Risk of thrombosis by administering an activated clotting factor
    d. Standard dose is 90 mcg/kg, but lower doses (e.g., 18–30 mcg/kg) have been documented to be effective and are significantly less expensive.
9. Massive transfusion protocols
    a. Indications – When to activate the protocol:
        i. 30%–40% blood volume loss with hypotension
        ii. 10 units of PRBCs in 24 hours
        iii. Transfuse entire blood volume in 24 hours
        iv. 50% blood volume replacement in 3 hours
        v. 3 or more units of PRBCs in 1 hour or 4 units of PRBCs in 4 hours, knowing the need to administer more
    b. Typical components – 1:1:1 of PRBCs, platelets, and FFP by volume
        i. Provides an Hct of 29%
        ii. Provides a Plt of 88,000/mm^3
        iii. Provides clotting factor activity of 62% of normal
        iv. May need to provide periodic units of cryoprecipitate
    c. Complications to monitor for:
        i. Dilution-induced thrombocytopenia
        ii. Citrate-induced hypocalcemia
        iii. Hyperkalemia
        iv. Acidosis

B. UFH (inhibits thrombin and some factor Xa)
   1. Protamine is an effective and rapid antidote for reversal of UFH.
      a. Basic protein derived from fish sperm that binds to heparin to form a stable salt
      b. Used to manage significant bleeding, reversal before surgery, or reversal of UFH administered during surgery (e.g., coronary artery bypass graft surgery)
      c. Dosing: 1 mg of protamine neutralizes approximately 100 units of heparin received in the past 2–2½ hours (maximum dose 50 mg), depending on the half-life of intravenous heparin of 60–90 minutes
      d. aPTT can be used to assess the effectiveness of UFH neutralization and need to redose protamine.
      e. Adverse effects
         i. Hypotension, bradycardia
         ii. Minimized by administering over slow intravenous infusion instead of intravenous push
         iii. Patients previously receiving protamine sulfate–containing insulin (i.e., NPH [neutral protein Hagedorn]) having undergone a vasectomy or having a known sensitivity to fish are at increased risk of having protamine antibodies and more likely to have allergic reactions.
         iv. If risk of allergic reaction is of concern, may pretreat with corticosteroids and/or antihistamines before protamine infusions
   2. Blood products may be needed in patients with significant bleeding.

C. LMWH (inhibits factor Xa and thrombin)
   1. No specific antidote is available for LMWH.
   2. Protamine
      a. Reverses about 50%–60% of the anticoagulant activity of LMWH
      b. Dosing
         i. 1 mg of protamine neutralizes about 100 anti-Xa units of LMWH (dalteparin).
         ii. 1 mg of protamine neutralizes about 1 mg of enoxaparin (1 mg enoxaparin = 100 anti-Xa units).
         iii. If LMWH dose was administered less than 8 hours before need for reversal, the following dose should be administered: 1 mg of protamine per 100 anti-Xa units (maximum dose 50 mg). May administer additional 0.5 mg of protamine per 100 anti-Xa units, if needed.
         iv. If LMWH dose was administered more than 8 hours before need for reversal, administer 0.5 mg of protamine for every 100 anti-Xa units.
   3. Recombinant factor VIIa as evaluated in small observational studies has been found effective and may be considered for management of significant bleeding when protamine fails.

D. Warfarin (VKA)
   1. Vitamin K (phytonadione or vitamin K_1) – Reverses the anticoagulant effect of warfarin. Because the anticoagulant effect of warfarin is mainly a result of the inhibition of vitamin K epoxide reductase, exogenous vitamin K can continue to be reduced and produce functional carboxylated clotting factors II, VII, IX, and X.
      a. Vitamin K reversal onset is delayed because several new clotting factors must be created to neutralize the effect of warfarin therapy.
         i. Oral vitamin K can take 24–48 hours to normalize the INR. This is the preferred route for managing INRs above the therapeutic range that are not associated with bleeding (Figure 1) or when reversal is needed before a planned surgical procedure.
         ii. Intravenous vitamin K can take 8–12 hours to normalize the INR, with full effects not seen until 24 hours. Should be administered as slow infusion over 20 minutes instead of intravenous "push" because of the risk of anaphylactoid allergic reactions. Intravenous vitamin K is preferred when managing major or life-threatening bleeding (Figure 1).

iii. Subcutaneous or intramuscular injection of vitamin K should be avoided because of delayed and erratic absorption in administering a fat-soluble vitamin into subcutaneous fat tissue and increased risk of hematoma development from intramuscular injection.

b. Of importance, aggressive vitamin K dosing can lead to difficulty in reinitiating warfarin therapy (warfarin resistance).

2. FFP vs. 4PCC – Historically, FFP has commonly been used for reversal of warfarin therapy in patients needing urgent surgery or when actively bleeding. However, more recent clinical data have shown that 4PCC provides much faster INR reversal than FFP.
   a. Similar concepts are described in the overview of 4PCCs as a reversal agent earlier in this section.
   b. A study of patients with acute major bleeding receiving warfarin (n=202) compared FFP (INR 3.6) with 4PCC (INR 3.9).
      i. Patients receiving 4PCC had their INR reversed to baseline within 30 minutes; FFP took about 8 hours to achieve the same INR.
      ii. Patients receiving FFP had more fluid overload because of the volume administered than did patients receiving 4PCC (5.8% vs. 12.8%). The treatment volume was more than 8 times greater with FFP than with 4PCC (813.5 vs. 99.4 mL).
      iii. More posttreatment thrombotic events occurred with 4PCC than with FFP (8.7% vs. 5.5%).
   c. Dosing (using actual body weight) – Only one 4PCC is available in the United States.
      i. INR 2 to less than 4: 25 units/kg with maximum dose of 2500 units
      ii. INR 4–6: 35 units/kg with maximum dose of 3500 units
      iii. INR greater than 6: 50 units/kg with maximum dose of 5000 units
      iv. Patients with an INR greater than 1.4 but less than 2.0 with cerebral bleeding may still receive 4PCC at a lower dose of 12.5–25 units/kg, but this approach was not part of the prospective study.
      v. Fixed doses of 4PCC (1000–1500 units) have also been investigated for major non-intracranial and intracranial hemorrhage, but data are limited to retrospective and observational studies.
   d. American College of Chest Physicians guidelines recommend a 4PCC over the FFP approach for the rapid reversal of warfarin therapy.

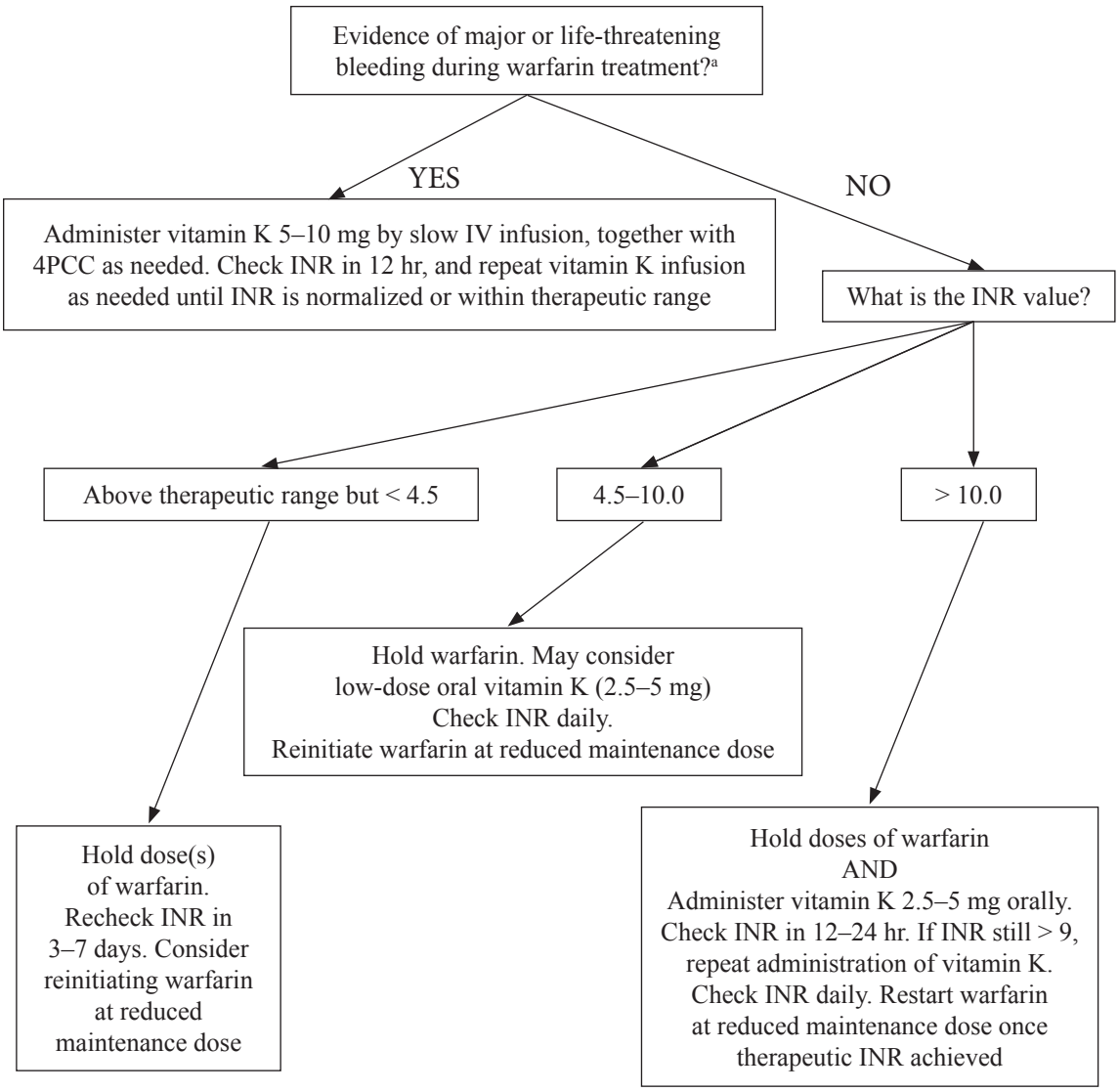

Evidence of major or life-threatening bleeding during warfarin treatment?[a]
YES
NO
Administer vitamin K 5–10 mg by slow IV infusion, together with 4PCC as needed. Check INR in 12 hr, and repeat vitamin K infusion as needed until INR is normalized or within therapeutic range
What is the INR value?
Above therapeutic range but < 4.5
4.5–10.0
> 10.0
Hold warfarin. May consider low-dose oral vitamin K (2.5–5 mg) Check INR daily. Reinitiate warfarin at reduced maintenance dose
Hold dose(s) of warfarin. Recheck INR in 3–7 days. Consider reinitiating warfarin at reduced maintenance dose
Hold doses of warfarin AND Administer vitamin K 2.5–5 mg orally. Check INR in 12–24 hr. If INR still > 9, repeat administration of vitamin K. Check INR daily. Restart warfarin at reduced maintenance dose once therapeutic INR achieved

Figure 1. Management of bleeding and/or elevated INRs with warfarin therapy.

[a]Bleeding at a critical site (e.g., intracranial hemorrhage, CNS hemorrhage, pericardial tamponade, intra-abdominal bleeding, retroperitoneal hemorrhage), hemodynamic instability, and/or clinically overt bleeding with an Hgb decrease of ≥ 2 g/dL or administration of ≥ 2 units of RBCs.

4PCC = 4-factor prothrombin complex concentrate; INR = international normalized ratio; IV = intravenous(ly).

E. Other Oral Anticoagulants
   1. For direct thrombin and Xa inhibitors, reversal before most procedures is not necessary as long as the drug is held for the appropriate number of days (Table 27 shows preoperative DOAC management).
   2. Vitamin K and protamine are not effective, and FFP cannot provide enough clotting factor replacement.
   3. aPCC at doses of 50 units/kg (maximum dose 200 units/kg) can normalize the aPTT, ecarin clotting time, and diluted thrombin time within 30 minutes.
   4. Activated charcoal may be used for a known recent (within 2–4 hours) ingestion.

Table 27. Preoperative DOAC Management

Drug	Preprocedural Holding Time
Dabigatran:	
Low/moderate[a] bleed risk procedures:	
CrCl ≥ 50 mL/min	1 day
CrCl < 50 mL/min	2 days
High[b] bleed risk procedures:	
CrCl ≥ 50 mL/min	2 days
CrCl < 50 mL/min	4 days
Apixaban, rivaroxaban, and edoxaban:	
Low/moderate[a] bleed risk procedures	1 day
High[b] bleed risk procedures	2 days

[a]Low/moderate bleed risk procedures include arthroscopy, foot/hand surgery, coronary angiography, GI endoscopy/colonoscopy, and abdominal hernia repair.

[b]High-bleed risk procedures include cancer surgery, major orthopedic surgery, genitourinary surgery, and cardiac intracranial or spinal surgery.

DOAC = direct oral anticoagulant.

5. Direct Thrombin Inhibitor (dabigatran)
    a. Although recombinant factor VIIa and aPCC may be used for reversal of dabigatran, these agents have shown mixed results. Guidelines recommend administration of PCC or aPCC if idarucizumab is not available.
    b. Idarucizumab – A specific antidote for direct thrombin inhibitor (e.g., dabigatran)
        i. Fully humanized antibody Fab portion with a 350-fold affinity for dabigatran compared with thrombin. Can take dabigatran out of circulation and the patient off thrombin to render it inactive
        ii. Administered at a total dose of 5 g intravenously
        iii. RE-VERSE-AD trial (n=503) evaluated patients receiving dabigatran with uncontrolled bleeding (group A; n=301) or requiring urgent surgery (group B; n=202) receiving 5 g of idarucizumab.
            (a) Primary outcome of the trial was the maximum percentage reversal of the anticoagulant effect of dabigatran within 4 hours of administering idarucizumab. Reversal was 100% in both groups for both assays. Full reversal occurred within 15 minutes and remained for 12–24 hours.
            (b) In group A, the most common sites of bleeding were GI (46%), intracranial hemorrhage (33%), and trauma (26%). Cessation of bleeding in patients without intracranial hemorrhage was a median of 2½ hours, with 68% having cessation within 24 hours.
            (c) In group B, the most common types of surgery were abdominal or infection (24%), fracture or septic arthritis (20%), and cardiovascular (18%). Periprocedural hemostasis was assessed by the investigators as normal in 93% of patients, mildly abnormal in 5%, and moderately abnormal in 2%, with no reports of severely abnormal hemostasis.
            (d) Thrombotic events occurred in 4.8% of patients within 30 days and 6.8% of patients within 90 days. Possible confounding variable of patients not being reinitiated on anticoagulant therapy in a timely fashion

6. Factor Xa Inhibitors (apixaban, rivaroxaban, edoxaban)
    a. Vitamin K and protamine are not effective, and FFP cannot provide enough clotting factor replacement.
    b. aPCC at doses of 25–50 units/kg can normalize the PT within 30 minutes. Data are limited to animal models and spiked blood samples.
    c. PCC: Has been used for reversal of a direct Xa inhibitor. Doses are typically 50 units/kg. Another option, with limited data, is to use a fixed dose of 2000 units as evaluated for warfarin reversal.
        i. One prospective study (n=66) showed a 24-hour hemostatic efficacy of 85%. These patients were, on average, 18 hours from their last dose of factor Xa inhibitor. Anti-Xa function was not assessed in these patients.
        ii. Another prospective study (n=77) showed a 24-hour hemostatic efficacy of 69%. Although the average time from the last dose was 12 hours, anti-Xa function was not assessed.
        iii. Small trials and limited participants have been evaluated, providing limited data to determine the thrombotic potential with this reversal strategy. Administration of supratherapeutic concentrations of clotting factors in patients who already require anticoagulant therapy suggests a risk exists.
    d. Coagulation factor Xa [recombinant], inactivated (also called andexanet alfa) – Specific antidote for factor Xa inhibitors
        i. Decoy factor Xa protein with high affinity for Xa inhibitors (also LMWH and fondaparinux)
            (a) Change in serine to alanine prevents catalytic activity and prevents the ability to convert prothrombin to thrombin.
            (b) GLA (carboxylation/γ-carboxyglutamic) domain is also removed. This prevents the ability to bind to a phospholipid membrane (platelets) and incorporation of the decoy protein into the prothrombinase complex.
        ii. Within minutes of the bolus, Xa concentrations return to baseline, where they remain throughout the rest of the infusion. Although anti-Xa activity returns to placebo concentrations within 2 hours once the infusion is discontinued, thrombin generation is maintained.
        iii. ANNEXA-4 (n=352) evaluated patients receiving a factor Xa inhibitor with an acute major bleed who received a bolus, followed by a 2-hour infusion of andexanet. Andexanet reversed the anti-Xa activity of apixaban and rivaroxaban by 92% and provided hemostatic efficacy of 82% within 12 hours.
            (a) The thrombotic event rate at the end of the ANNEXA-4 trial was 10% at 30 days.
            (b) Only 2% of patients receiving any anticoagulant developed a thrombotic event, and no patient receiving oral anticoagulation developed a thrombotic event.
        iv. Low-dose andexanet is a 400-mg intravenous bolus, followed by 4 mg/minute for 2 hours. This dose is indicated for patients with (1) the last dose of apixaban of 5 mg or less or 10 mg or less of rivaroxaban dose administered less than 8 hours earlier or timing unknown or (2) the last dose of apixaban or rivaroxaban administered 8 hours or more earlier.
        v. High-dose andexanet is an 800-mg intravenous bolus, followed by 8 mg/minute for 2 hours. This dose is indicated for patients with (1) the last dose of apixaban greater than 5 mg or rivaroxaban greater than 10 mg taken less than 8 hours earlier or timing unknown or (2) an unknown dose of apixaban or rivaroxaban.
    e. Not currently indicated for reversal of edoxaban, enoxaparin, or fondaparinux. In addition, only indicated for life-threatening bleeding and not for patients requiring urgent surgery

Patient Cases

9. A 49-year-old male (height 175 cm, weight 100 kg) was diagnosed with an idiopathic DVT 3 weeks ago. He currently takes warfarin 8 mg orally daily. He missed his INR readings last week when he went on a short vacation. Today, his INR is 10.4. He is not currently bleeding and has no risk factors for bleeding. In addition to holding his warfarin dose, which is the best initial strategy for managing this patient's high INR?

   A. Hold warfarin only.

   B. Hold warfarin and administer 4PCC 50 units/kg intravenously.

   C. Hold warfarin and administer vitamin K 5 mg orally.

   D. Hold warfarin and administer vitamin K 10 mg intravenously.

10. A 58-year-old male is receiving enoxaparin 40 mg subcutaneously daily for VTE prophylaxis. While trying to shave himself at 6 p.m., he cuts his neck, and the medical team cannot stop the bleeding. His last enoxaparin dose was administered at 8 a.m. Which would be the most appropriate protamine dose (in milligrams) for this patient?

   A. 10.

   B. 20.

   C. 40.

   D. 50.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: B

This patient's CHA_2DS_2-VASc score is 3: 1 point for age 65–74 years (73 years), 1 point for hypertension, and 1 point for heart failure (Answer B is correct). A score of 2 (Answer A) would be correct when using the $CHADS_2$ score instead of the CHA_2DS_2-VASc score because his age would not give any points in the $CHADS_2$ score. The patient's history of stable ischemic heart disease may be assumed to be 1 point for vascular disease, but this is only 1 point in patients with a prior MI, peripheral artery disease, or aortic disease, making Answer C incorrect. Given his score of 3, Answer D would also be incorrect.

2. Answer: B

Only dabigatran significantly reduced ischemic stroke in the RE-LY trial (Answer A is incorrect). The benefit of the DOACs in each of their respective trials was a significant reduction in hemorrhagic stroke. This drove the overall benefit and safety for all the agents (hemorrhagic stroke is counted as an efficacy and safety end point in all the trials) (Answer B is correct). Although clinicians may reach the conclusions in Answer C, evidence is insufficient to make this claim; cross-trial comparisons are inappropriate because of the different risks of patients studied and the different sample sizes of the trials. The 0.3% absolute difference in the ARISTOTLE and ROCKET-AF trials makes it difficult to conclude that one agent is more efficacious than the other without a head-to-head randomized controlled trial. Answer D is also incorrect because bleeding was similar to warfarin in the RE-LY trial with dabigatran and lower with edoxaban in the ENGAGE trial. Despite these data, the bleeding rates in the trials cannot be compared because of the different times in which bleeding events were accrued in the trials.

3. Answer: C

Given the patient's CHA_2DS_2-VASc score of 3, he is at high risk of ischemic stroke and should receive anticoagulation. The patient's CrCl is about 40 mL/minute using the Cockcroft-Gault equation with total body weight. Although any of the agents listed would be acceptable in this patient, not all of the dosing regimens are correct. The dabigatran dose should not be reduced from 150 mg twice daily to 75 mg twice daily until the CrCl is less than 30 mL/minute, making Answer A incorrect. Both rivaroxaban and edoxaban should be dose reduced when the CrCl is less than 50 mL/minute in patients with nonvalvular AF. Rivaroxaban should be reduced from 20 mg daily to 15 mg daily, and edoxaban should be reduced from 60 mg daily to 30 mg daily, making Answers B and D incorrect. Apixaban is listed at the typical dose and is not reduced to 2.5 mg daily unless the patient meets two of three criteria (age 80 or older, weight 60 kg or less, or SCr 1.5 mg/dL or greater). This patient has the elevated SCr, but his age and weight do not meet these criteria. Therefore, full-dose apixaban is correct (Answer C) for this patient.

4. Answer: A

Trials to date have mainly evaluated the safety of the listed regimens. Answer D would not be supported by the currently available evidence until dosing or safety data become available. Answer B would be incorrect because the apixaban dose evaluated in the AUGUSTUS trial was 5 mg twice daily. Answer A (rivaroxaban plus clopidogrel) and Answer C (warfarin, aspirin, and clopidogrel) were compared in the PIONEER AF-PCI trial, with the rivaroxaban regimen significantly reducing clinically relevant bleeding. Because of better safety, Answer A is correct and Answer C is incorrect. The 10-mg dose of rivaroxaban is correct because the patient's CrCl is 40 mL/minute. In the trial, patients with a CrCl of 30–50 mL/minute received rivaroxaban 10 mg daily instead of 15 mg daily.

5. Answer: D

In patients receiving a mechanical heart valve, only those with an indication for antiplatelet therapy need to have aspirin therapy added to their regimen, making Answers A and B incorrect. Answer C is the INR goal for a mechanical aortic valve and is therefore incorrect. Because of the higher thrombotic risk of a mitral valve than an aortic valve, the INR goal should be higher, making Answer D correct.

6. Answer: D

Answer A is incorrect because mechanical valves have a higher risk of thrombosis than bioprosthetic valves. This is shown by the class 1 recommendation for warfarin therapy for mechanical heart valves compared with aspirin therapy for bioprosthetic valves. The highest risk of thrombosis with a bioprosthetic valve is during

the first 3 months after valve placement, not out to 1 year, making Answer B incorrect. Answer C is also incorrect; although patients with a mechanical mitral valve and those with an aortic valve with risk factors for TE should receive bridge therapy during invasive procedures, patients with a bileaflet mechanical aortic valve and no risk factors for TE need not receive bridge therapy. Answer D is correct; because of the larger valve size and slower flow through the mitral valve than through the aortic valve, mitral valves carry a higher risk of thrombosis. This is shown by the more aggressive anticoagulant regimen, regardless of the type of valve used (bioprosthetic or mechanical).

7. Answer: C

This patient has several risk factors for VTE with a calculated Padua score of 7 and requires prophylaxis (Answer D is incorrect). Although fondaparinux is effective and safe for VTE prophylaxis in medically ill patients, the appropriate dose is 2.5 mg subcutaneously daily, not 5 mg daily (Answer A is incorrect). Although apixaban has been studied for VTE prophylaxis, it lacked efficacy and safety when evaluated for extended prophylaxis (Answer B is incorrect). Several studies have shown the efficacy and safety of enoxaparin 40 mg subcutaneously once daily for VTE prophylaxis in medically ill patients (Answer C is correct).

8. Answer: D

This patient can be treated for his DVT event without receiving injectable anticoagulation. Both rivaroxaban and apixaban provide this ability. Because edoxaban requires at least 5 days of injectable therapy before initiation and warfarin must be bridged with injectable anticoagulation for at least 5 days, Answers B and C are incorrect. The rivaroxaban regimen in Answer A is the standard regimen, but the patient is taking a protease inhibitor. Protease inhibitors, especially ritonavir, are potent P-gp and CYP3A4 inhibitors and are contraindicated with the use of rivaroxaban, making Answer A incorrect. Although the typical apixaban regimen for VTE treatment is 10 mg twice daily for 7 days followed by 5 mg twice daily, patients receiving potent P-gp and CYP3A4 inhibitors can still use apixaban but at a 50% dose reduction, making Answer D correct.

9. Answer: C

Because this patient is not bleeding and rapid reversal is unnecessary, 4PCC is not needed (Answer B is incorrect). The patient's lack of bleeding also makes high-dose (10 mg) intravenous vitamin K unnecessary (Answer D is incorrect). For an INR over 10 with no bleeding, the dose of oral vitamin K should be 5 mg, making Answer C correct and Answer A (simply holding the warfarin dose without a reversal agent) incorrect.

10. Answer: B

Protamine is acceptable for the reversal of enoxaparin therapy because it reverses about 50%–60% of the anticoagulant effect of LMWH. One milligram of protamine will reverse 100 anti-Xa units of LMWH. One milligram of enoxaparin equals 100 anti-Xa units. Thus, 1 mg of protamine will reverse 1 mg of enoxaparin. Typically, a dose of 40 mg of protamine would be used to reverse a dose of 40 mg of enoxaparin. However, when the last dose of enoxaparin is more than 8 hours before the need for protamine, one-half the dose should be administered. Therefore, a dose of 20 mg of protamine (Answer B is correct) would be appropriate in this patient, not a dose of 40 mg (Answer C is incorrect). The dose of 10 mg would be too low for this setting, making Answer A incorrect. Although 50 mg of protamine (Answer D) is the maximum dose to be administered at one time, it is more than twice as much protamine as would be required in this patient setting and is incorrect.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: B

This patient with nonvalvular AF has three risk factors for stroke, according to the CHA_2DS_2-VASc score: 1 point for age 65–74 years (72 years old), 1 point for hypertension, and 1 point for female sex. Answer A is incorrect because she would have a score of 1 using the $CHADS_2$ score, which would be from hypertension, but that scoring system does not give a point for age unless the patient is 75 or older and gives no points for being female. Her HAS-BLED score is 1 for age older than 65. Although Answer D has the correct CHA_2DS_2-VASc score, the HAS-BLED score is incorrect. Even though the patient has hypertension for HAS-BLED, the systolic blood pressure needs to be greater than 160 mm Hg for it to receive 1 point. Therefore, her score is only 1, not 2 as in Answer D. Answer C is also incorrect because it overcalculates both the CHA_2DS_2-VASc score and the HAS-BLED score. Because the patient's CHA_2DS_2-VASc score is 3 and HAS-BLED score is 1, Answer B is correct. This patient is a candidate for anticoagulant therapy because of stroke risk and has an acceptable bleeding risk from warfarin therapy.

2. Answer: B

Given the patient's CHA_2DS_2-VASc score of 3 and lack of contraindications to anticoagulant therapy, she is at high risk of ischemic stroke and needs anticoagulant therapy, making Answer A incorrect. Apixaban would be acceptable, but the reduced dose of 2.5 mg twice daily is only for patients with two high-risk bleeding features (age 80 or older, weight 60 kg or less, or SCr 1.5 mg/dL or greater). She has one risk factor with weight less than 60 kg (57 kg), but age (72 years) and SCr (0.8 mg/mL) do not meet the criteria. Therefore, she should receive apixaban 5 mg twice daily, making Answer C the incorrect apixaban dose. Answer D is incorrect because the correct edoxaban dose for this patient would be 60 mg daily. Rivaroxaban is only dose reduced when the CrCl is less than 50 mL/minute. Because this patient's renal function is above that level, Answer B is correct for using the correct dose of anticoagulant.

3. Answer: D

Answer A is incorrect; although protamine is an antidote for UFH and a partial antidote for LMWH, it would not be expected to reverse a direct thrombin inhibitor. Answer B is incorrect; FFP does not provide enough clotting factors to reverse a direct thrombin inhibitor. Idarucizumab is a fully humanized antibody to dabigatran and will bind dabigatran more strongly than thrombin. Idarucizumab is an effective reversal agent for dabigatran (Answer D is correct). Answer C is incorrect; Coagulation factor Xa [recombinant], inactivated is a recombinant factor Xa that binds factor Xa inhibitors but does not affect the direct thrombin inhibitor, dabigatran.

4. Answer: A

Patients with a bioprosthetic surgical aortic or mitral valve who are at low risk of bleeding can receive warfarin for at least 3 months, up to 6 months, but the INR target is 2.0–3.0. The higher INR goal of 2.5–3.5 is for a patient receiving a mechanical mitral valve. In addition, the initial warfarin dose is too high for a patient who is taking amiodarone. A more appropriate starting dose would be 2 mg or 2.5 mg daily. Therefore, Answer B is incorrect for several reasons. Neither DOAC would be used unless the patient had concomitant AF. Although data are limited, it is generally thought that patients with AF with bioprosthetic valves can receive therapy with a DOAC. This patient does not have AF and does not require anticoagulation for the valve, making Answers C and D incorrect. Answer A, low-dose aspirin, is all that is indicated because of the lower thrombogenic potential of a bioprosthetic valve compared with a mechanical valve.

5. Answer: D

According to the 2020 ACC/AHA guidelines, indefinite low-dose aspirin therapy is indicated for patients receiving a bioprosthetic aortic or mitral valve, making Answer D correct. The duration in Answer A is too short and might be confused with the duration of dual antiplatelet therapy in patients with a bare metal stent. Answer B would be the minimal therapy duration if the patient were receiving warfarin therapy for this bioprosthetic surgical aortic valve. Answer C is also incorrect and might be confused with the duration of dual antiplatelet therapy for patients receiving a drug-eluting stent.

6. Answer: C

This patient has five risk factors for developing VTE: age older than 40 (51 years), obesity (BMI 36 kg/m^2), recent surgery, immobility, and person who smokes, making Answer C correct and Answers A, B, and D incorrect.

7. Answer: C

Answer B is incorrect because the duration of higher-intensity rivaroxaban should be 21 days, not 7 days. Apixaban's duration of higher-intensity therapy is 7 days. Answer D is incorrect because the UFH dosing is insufficient. This is the dosing in patients with an acute coronary syndrome. Patients receiving dabigatran or edoxaban must first receive at least 5 days of injectable therapy. The dosing of enoxaparin and the DOAC is correct in both Answers A and C, but the DOAC should not be overlapped with the injectable anticoagulant, making Answer A incorrect and Answer C correct.

8. Answer: B

Protamine 50 mg is the correct dose for this patient. To calculate the dose, add the amount of UFH administered in the past 2½ hours, which gives a total of 5000 units of UFH. A dose of 1 mg of protamine for every 100 units of UFH equals a protamine dose of 50 mg (Answer B is correct). Because the bolus dose was administered more than 3 hours ago, it is not part of the calculation. Although 100 units would be the calculated dose according to the bolus, the bolus was administered too long ago to be considered (Answer A is incorrect). The doses of 11.25 and 22.5 mg are incorrect because they consider only the amount of UFH received in the past 30 and 60 minutes, respectively, not the past 2–2½ hours (Answers C and D are incorrect).

9. Answer: C

Although dabigatran can be used for VTE prevention in patients with hip replacement surgery, it is not indicated in patients with hip fracture surgery, making Answer A incorrect. The correct enoxaparin dose for hip fracture surgery is 30 mg subcutaneously twice daily or enoxaparin 40 mg subcutaneously every 12 hours, making Answer B incorrect. Edoxaban is not indicated for orthopedic surgery in the United States. All studies with edoxaban were done only in Japan, making Answer D incorrect. Answer C is correct because this is the correct dosing of fondaparinux for orthopedic surgical procedures.

Infectious Diseases I

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Learning Objectives

1. Identify the presenting signs and symptoms, etiology, and risk factors of respiratory tract infections, urinary tract infections, skin and soft tissue infections, osteomyelitis, central nervous system (CNS) infections, intra-abdominal infections, *Clostridioides difficile* infections, and endocarditis.
2. Recommend appropriate treatment for patients with respiratory tract infections, urinary tract infections, skin and soft tissue infections, osteomyelitis, CNS infections, intra-abdominal infections, *C. difficile* infections, and endocarditis.
3. Select appropriate preventive therapy for urinary tract infections, CNS infections, endocarditis, and surgical wound infections.

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

1. P.E. is a 56-year-old man who comes to the clinic with a 3-day history of fever, chills, pleuritic chest pain, malaise, and productive cough. In the clinic, his temperature is 102.1°F (38.9°C) (all other vital signs are normal). His chest radiograph reveals consolidation in the right lower lobe. His white blood cell count (WBC) is 14,400 cells/mm^3, but all other laboratory values are normal. He is given a diagnosis of community-acquired pneumonia (CAP). He has not received any antibiotics in 5 years and has no chronic disease states. Which is the best empiric therapy for P.E.?
   A. Doxycycline 100 mg orally twice daily.
   B. Cefuroxime axetil 250 mg orally twice daily.
   C. Levofloxacin 750 mg orally daily.
   D. Trimethoprim/sulfamethoxazole double strength orally twice daily.

2. H.W. is a 38-year-old woman who presents with a fever, malaise, dry cough, nasal congestion, and severe headaches. Her symptoms began suddenly 3 days ago, and she has been in bed since then. She reports no other illness in her family, but several people have recently called in sick at work. It is influenza season. Which is best for H.W.?
   A. Azithromycin 500 mg, followed by 250 mg daily orally for 4 more days.
   B. Amoxicillin/clavulanic acid 875 mg orally twice daily for 5 days.
   C. Oseltamivir 75 mg twice daily orally for 5 days.
   D. Symptomatic treatment only.

3. A study is designed to assess the risk of pneumococcal pneumonia in older adults 10 years or more after receiving their last pneumococcal vaccination, compared with older adults who have never received any pneumococcal vaccinations. Which study design is best?
   A. Case series.
   B. Case-control study.
   C. Prospective cohort study.
   D. Randomized controlled trial.

4. A.B. is a 63-year-old woman who presents to the emergency department with left leg pain and erythema. The pain and erythema have worsened over the past 24 hours. The left leg is significantly swollen with a large area of erythema and large bullae extending from the thigh to the upper leg. There is crepitus within the soft tissue. A.B. is found to have rapidly progressing necrotizing fasciitis. A.B. has normal renal function and no known drug allergies. Which is the best empiric therapy for A.B.?
   A. Vancomycin 15 mg/kg intravenously every 12 hours.
   B. Piperacillin/tazobactam 4.5 g intravenously every 8 hours.
   C. Vancomycin 15 mg/kg intravenously every 12 hours plus meropenem 1 g intravenously every 8 hours plus clindamycin 900 mg intravenously every 8 hours.
   D. Linezolid 600 mg intravenously every 12 hours plus ceftriaxone 1 g intravenously every 24 hours plus azithromycin 500 mg intravenously daily.

5. N.R. is a 28-year-old woman who presents to the clinic with a 2-day history of dysuria, frequency, and urgency. She has no significant medical history, and the only drug she takes is an oral contraceptive. Which is the best empiric therapy for N.R.?
   A. Nitrofurantoin extended release (ER) 100 mg orally twice daily for 3 days.
   B. Ciprofloxacin 500 mg orally twice daily for 7 days.
   C. Trimethoprim/sulfamethoxazole double strength orally twice daily for 3 days.
   D. Cephalexin 500 mg orally four times daily for 3 days.

6. B.Y. is an 85-year-old woman who is bedridden and lives in a nursing home. She is chronically catheterized, and her urinary catheter was last changed 3 weeks ago. Today, her urine is cloudy, and a urinalysis reveals many bacteria. B.Y. is not noticing any symptoms. A urine culture is obtained. Which option is best for B.Y.?
   A. No antibiotic therapy because she is chronically catheterized and has no symptoms.
   B. No antibiotic therapy, but the catheter should be changed.
   C. Ciprofloxacin 500 mg orally twice daily for 7 days and change the catheter.
   D. Ciprofloxacin 500 mg orally twice daily for 14–21 days without a change in catheter.

7. V.E. is a 44-year-old man who presents to the emergency department with a warm, erythematous, and painful right lower extremity. There is no raised border at the edge of the infection. Three days ago, he scratched his leg on a barbed wire fence on his property (no puncture wound associated with the fence). His temperature has been as high as 101.8°F (38°C) with chills. Doppler studies of his lower extremity are negative. Blood cultures are negative. Which is the best empiric therapy for V.E.?
   A. Cefazolin 1 g intravenously every 8 hours.
   B. Penicillin G 2 million units intravenously every 4 hours.
   C. Piperacillin/tazobactam 3.375 g intravenously every 6 hours.
   D. Doxycycline 100 mg orally twice daily.

8. R.K. is a 36-year-old woman who presents to the emergency department with a severe headache and neck stiffness. Her temperature is 99.5°F (37.5°C). After a negative computed tomographic scan of the head, a lumbar puncture reveals the following: glucose 54 mg/dL (peripheral, 104 mg/dL), protein 88 mg/dL, and WBC 220 cells/mm^3 (100% lymphocytes). The Gram stain reveals no organisms. Which option is best for R.K.?
   A. This is aseptic meningitis, and no antibiotics are necessary.
   B. Administer ceftriaxone 2 g intravenously every 12 hours until the cerebrospinal fluid (CSF) cultures are negative for bacteria.
   C. Administer ceftriaxone 2 g intravenously every 12 hours and vancomycin 15 mg/kg intravenously every 12 hours until the CSF cultures are negative for bacteria.
   D. Administer acyclovir 500 mg intravenously every 8 hours until the CSF culture results are negative for bacteria.

9. L.G. is a 49-year-old woman with a history of mitral valve prolapse. She presents to her physician's office with malaise and a low-grade fever. Her physician notes that her murmur is louder than usual and orders blood cultures and an echocardiogram. A large vegetation is observed on L.G.'s mitral valve, and her blood cultures are growing *Enterococcus faecalis* (susceptible to all antibiotics). Which is the best therapy for L.G.?
   A. Penicillin G plus gentamicin for 2 weeks.
   B. Vancomycin plus ceftriaxone for 2 weeks.
   C. Ampicillin plus ceftriaxone for 6 weeks.
   D. Cefazolin plus gentamicin for 4–6 weeks.

10. N.L. is a 28-year-old woman with no significant medical history. She reports to the emergency department with fever and severe right lower quadrant abdominal pain. The pain had been dull for the past few days, but it suddenly became severe during the past 8 hours. Her temperature is 103.5°F (39.7°C), and she has rebound tenderness on abdominal examination. She is taken to surgery immediately, where a perforated appendix is diagnosed and repaired. Which is the best follow-up antibiotic regimen?

A. Vancomycin 1000 mg intravenously every 12 hours plus metronidazole 500 mg intravenously every 8 hours.
B. Cefazolin 1 g intravenously every 8 hours plus ciprofloxacin 400 mg intravenously every 12 hours.
C. Ceftriaxone 1 g intravenously every 24 hours plus metronidazole 500 mg intravenously every 8 hours.
D. No antibiotics needed after surgical repair of a perforated appendix.

11. O.R. is a 73-year-old man who presents to the emergency department with a 3-day history of fever, chills, frequency, urgency, and perineal pain. A urinalysis reveals many bacteria. A rectal examination reveals a swollen, tender prostate. He is given a diagnosis of acute bacterial prostatitis. Which is the best regimen for this patient?
A. Amoxicillin/clavulanate 875 orally twice daily for 14 days.
B. Trimethoprim/sulfamethoxazole double strength orally twice daily for 7 days.
C. Cefprozil 500 mg orally twice daily for 21 days.
D. Ciprofloxacin 500 mg orally twice daily for 28 days.

12. J.M. is a 72-year-old woman with a history of atrial fibrillation, hypertension, a right total hip replacement 8 months earlier, and Crohn disease. She has no drug allergies. She presents to the hospital with increasing pain in her prosthetic hip over the past month. There is concern about hip osteomyelitis. Bone cultures are growing methicillin-sensitive *Staphylococcus aureus*. J.M. has normal renal function and no known drug allergies. Which is the best antibiotic regimen for this patient?
A. Vancomycin 1000 mg intravenously every 12 hours plus rifampin 300 mg orally twice daily for 2 weeks.
B. Cefazolin 2 g intravenously every 8 hours plus rifampin 300 mg orally twice daily for 6 weeks followed by long-term oral antibiotics.
C. Nafcillin 1 g intravenously every 4 hours for 6 weeks.
D. Daptomycin 6 mg/kg intravenously daily for 6 weeks followed by long-term oral antibiotics.

13. B.K. is a 58-year-old woman (height 66 inches, weight 82 kg) who is scheduled to undergo a total knee replacement tomorrow. She has no significant medical history and no drug allergies. Which is the best surgical prophylaxis regimen for this patient?
A. Cefazolin 2 g within 1 hour of the incision and no doses postoperatively.
B. Cefazolin 2 g within 4 hours of the incision and three doses every 8 hours postoperatively.
C. Cefazolin 1 g within 1 hour of the incision and three doses every 8 hours postoperatively.
D. Cefazolin 1 g within 4 hours of the incision and no doses postoperatively.

BPS Pharmacotherapy Specialty Examination Content Outline

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline, tested during the Spring 2024 window:

1. Patient-Centered Pharmacotherapy
   a. 1.1. Develop patient-centered, evidence-based pharmacotherapy plans. Subtasks: 1.1.1 – 1.1.3, 1.1.6, 1.1.8, 1.1.10, 1.1.11, 1.1.13, 1.1.14.
   b. 1.2. Monitor the patient to ensure safe and effective pharmacotherapy. Subtasks: 1.2.1, 1.2.2, 1.2.4.
   c. 1.3. Modify pharmacotherapy plans through ongoing patient assessment. Subtasks: 1.3.1 – 1.3.5.
2. Healthcare Systems and Population Health
   a. 3.3. Incorporate public health initiatives to improve population health. Subtask: 3.3.1.

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline, tested starting Fall 2024:

1. Patient Care Specialty Areas
   a. 1A. Primary Pharmacotherapy Specialty Areas. Subtasks: 1A1.
2. Therapeutics and Patient Management
   a. 2A. Treatment Planning. Subtasks: 2A1 – 2A5.
   b. 2B. Therapeutic Implementation. Subtasks: 2B1, 2B2.
   c. 2C. Treatment Outcomes and Monitoring. Subtasks: 2C1 – 2C4.
3. Professional Practice
   a. 3A. Quality of Care. Subtasks: 3A1, 3A2, 3A4.
   b. 3C. Practice Management. Subtasks: 3C1, 3C2.

I. RESPIRATORY TRACT INFECTIONS

A. Pneumonia
   1. Pneumonia is the most common cause of death attributable to infectious diseases (very high mortality rate in older adults) and in the top 10 causes of death in the United States.
   2. Hospital-acquired pneumonia (HAP) is the second most common nosocomial infection (0.6%–1.1% of all hospitalized patients). There is a higher incidence in patients in the intensive care unit, recovering from thoracic or upper abdominal surgery, and in older adults.
   3. Mortality rates
      a. Community-acquired pneumonia (CAP) without hospitalization: Less than 1%
      b. CAP with hospitalization: About 14%
      c. Ventilator-associated pneumonia (VAP): About 20%–50%

B. Community-Acquired Pneumonia
   1. Definition: Acute infection of the pulmonary parenchyma, accompanied by an acute infiltrate consistent with pneumonia on chest radiograph or auscultatory findings, acquired in the community or within 48 hours of hospitalization.
   2. Symptoms of CAP are listed below. Older adults often have fewer and less severe findings (mental status changes are common).
      a. Fever or hypothermia
      b. Rigors
      c. Sweats
      d. New cough with or without sputum (90%)
      e. Chest discomfort (50%)
      f. Onset of dyspnea (66%)
      g. Fatigue
      h. Myalgias
      i. Abdominal pain
      j. Anorexia
      k. Headache
   3. Hospitalization should be based on a clinical prediction rule for prognosis (e.g., a pneumonia severity index [PSI] score greater than 90 indicates inpatient management).
   4. Admission to the ICU or a general medicine floor should be based on a clinical prediction rule for prognosis (e.g., 2007 Infectious Diseases Society of America/American Thoracic Society [IDSA/ATS] criteria for defining severe community-acquired pneumonia – Table 1).

Table 1. 2007 IDSA/ATS Criteria for Defining Severe Community-Acquired Pneumonia[a]

Major Criteria	Minor Criteria
Septic shock with need for vasopressors	Respiratory rate > 30 breaths/min
Respiratory failure requiring mechanical ventilation	Pa_{O_2}/F_{IO_2} ratio ≤ 250
	Multilobar infiltrates
	Confusion/disorientation
	Uremia (BUN ≥ 20 mg/dL)
	Leukopenia[b] (WBC < 4.0×10^3 cells/mm^3)
	Thrombocytopenia (Plt < 100,000/mm^3)
	Hypothermia (temperature < 36°C)
	Hypotension requiring aggressive fluid resuscitation

[a]Higher level of care if either one major criterion or three or more minor criteria.

[b]Related to infection rather than other factors (e.g., chemotherapy).

F_{IO_2} = fraction of inspired oxygen.

C. HAP and VAP
   1. HAP: Pneumonia in a nonventilated patient that occurs 48 hours or more after admission and was not incubating at the time of admission
   2. VAP: Pneumonia that arises more than 48 hours after endotracheal intubation
   3. Risk factors for hospital-acquired pneumonia
      a. Intubation and mechanical ventilation
      b. Supine patient position
      c. Enteral feeding
      d. Oropharyngeal colonization
      e. Stress ulcer prophylaxis
      f. Blood transfusion
      g. Hyperglycemia
      h. Immunosuppression or corticosteroids
      i. Surgical procedures: thoracoabdominal, upper abdominal, thoracic
      j. Immobilization
      k. Nasogastric tubes
      l. Previous antibiotic therapy
      m. Admission to the intensive care unit
      n. Advanced age
      o. Underlying chronic lung disease

D. Microbiology (Table 2)

Table 2. Incidence of Pneumonia by Organism

Community Acquired (%)		Hospital Acquired (%)	
Unidentifiable	40–60	Unidentifiable	50
Mycoplasma pneumoniae	13–37	*S. aureus*	10
Streptococcus pneumoniae	9–20	*Pseudomonas aeruginosa*	8
Haemophilus influenzae	3–10	*Enterobacter* spp.	5
Chlamydia pneumoniae	1–17	*K. pneumoniae*	4
Legionella pneumophila	0.7–13	*Acinetobacter* spp.	2
Viruses	Common	*Serratia marcescens*	2
Others:	Uncommon	*Escherichia coli*	2
Staphylococcus aureus		*S. pneumoniae*	1
Moraxella catarrhalis			
Anaerobes			
Gram-negative bacilli (e.g., *Klebsiella pneumoniae*)			
Specific populations in community-acquired pneumonia:		Issues in hospital-acquired pneumonia:	
Alcoholism: *S. pneumoniae,* oral anaerobes, gram-negative bacilli (e.g., *Klebsiella*)		*P. aeruginosa* is transmitted by health care workers' hands or respiratory equipment	
Nursing home: *S. pneumoniae, H. influenzae,* gram-negative bacilli, *S. aureus*		*S. aureus* is transmitted by health care workers' hands	
COPD: *S. pneumoniae, H. influenzae, M. catarrhalis*		Enterobacterales endogenously colonize hospitalized patients' airways (healthy people seldom have gram-negative upper airway colonization)	
Postinfluenza: *H. influenzae, S. aureus, S. pneumoniae*		Stress changes respiratory epithelial cells so that gram-negative organisms can adhere	
Exposure to water: *Legionella*		Up to 70% of patients in the intensive care unit have gram-negative upper airway colonization, and 25% of them become infected through aspiration	
HIV infection: *Pneumocystis jirovecii, S. pneumoniae, M. pneumoniae, Mycobacterium*			

COPD = chronic obstructive pulmonary disease; HIV = human immunodeficiency virus.

Patient Case

1. R.L. is a 68-year-old man who presents to the emergency department with coughing and shortness of breath. His symptoms, which began 4 days ago, have worsened during the past 24 hours. He is coughing up yellow-green sputum, and he has chills, with a temperature of 102.4°F (39°C). His medical history includes coronary artery disease with a myocardial infarction 5 years ago, congestive heart failure, hypertension, and osteoarthritis. He rarely drinks alcohol and has not smoked since his myocardial infarction. He lives at home with his wife. His medications on admission include lisinopril 10 mg/day, hydrochlorothiazide 25 mg/day, and acetaminophen 650 mg four times/day. On physical examination, he is alert and oriented, with the following vital signs: temperature 101.8°F (38°C), heart rate 100 beats/minute, respiratory rate 32 breaths/minute, and blood pressure 142/94 mm Hg. His laboratory results are normal except for blood urea nitrogen (BUN) 32 mg/dL (serum creatinine [SCr] 1.23 mg/dL). A chest radiograph reveals infiltrates in the right lower lobe. A sputum specimen is not available. If R.L. were hospitalized, which would be the best empiric therapy for him?
   A. Ampicillin/sulbactam 3 g intravenously every 6 hours.
   B. Piperacillin/tazobactam 4.5 g intravenously every 6 hours plus gentamicin 180 mg intravenously every 12 hours.
   C. Ceftriaxone 2 g intravenously every 24 hours plus azithromycin 500 mg intravenously every 24 hours.
   D. Doxycycline 100 mg intravenously every 12 hours.

E. Therapy: Pneumonia
   1. CAP
      a. Empiric treatment of nonhospitalized patients
         i. No comorbidities or risk factors for methicillin-resistant *Staphylococcus aureus* (MRSA) or *Pseudomonas aeruginosa*
            (a) Amoxicillin (dosing 1 g three times daily)
            (b) Doxycycline
            (c) Macrolide (clarithromycin or azithromycin) if local pneumococcal resistance to macrolides is less than 25%
         ii. Comorbidities (chronic obstructive pulmonary disease [COPD], diabetes, alcoholism, chronic renal or liver failure, congestive heart failure, malignancy, asplenia, or immunosuppression)
            (a) Respiratory fluoroquinolone (moxifloxacin or levofloxacin dosing 750 mg once daily)
            (b) Macrolide or doxycycline with amoxicillin/clavulanate or cefpodoxime or cefuroxime
      b. Empiric treatment of hospitalized patients with non-severe pneumonia (may need to add other antibiotics if the patient has risk factors for *P. aeruginosa* or MRSA)
         i. Respiratory fluoroquinolone (moxifloxacin or levofloxacin)
         ii. β-Lactam (ampicillin/sulbactam, ceftriaxone, or ceftaroline) plus a macrolide (or doxycycline)
      c. Empiric treatment of hospitalized patients with severe pneumonia necessitating intensive care unit treatment (may need to add other antibiotics if the patient has risk factors for *P. aeruginosa* or methicillin-resistant *S. aureus* [MRSA])
         i. Ampicillin/sulbactam plus either a respiratory fluoroquinolone or a macrolide
         ii. Ceftriaxone plus either a respiratory fluoroquinolone or a macrolide
         iii. Ceftaroline plus either a respiratory fluoroquinolone or a macrolide
      d. Treatment duration: At least 5 days; duration should be guided by a validated measure of clinical stability (resolution of vital sign abnormalities, ability to eat, and normal mentation)

2. CAP and Risk Factors for MRSA or *P. aeruginosa*
    a. Treat with CAP guideline regimens.
    b. Additional antibiotics with MRSA activity
        i. Include if prior respiratory isolation of MRSA
        ii. Include if patient has severe pneumonia and locally validated risk factors for MRSA (especially hospitalization and parenteral antibiotics given in past 90 days)
        iii. Vancomycin or linezolid
    c. Additional antibiotics with *Pseudomonas* activity
        i. Include if prior respiratory isolation of *P. aeruginosa*
        ii. Include if patient has severe pneumonia and locally validated risk factors for *P. aeruginosa* (especially hospitalization and parenteral antibiotics given in past 90 days).
        iii. Piperacillin/tazobactam, cefepime, ceftazidime, imipenem, meropenem, or aztreonam
    d. Therapy with additional antibiotics should be de-escalated on the basis of culture results, respiratory rapid diagnostic test results (e.g., MRSA nasal PCR), and clinical improvement.

Patient Case

2. B.P. is a 66-year-old woman who underwent a two-vessel coronary artery bypass graft 8 days ago and has been on a ventilator in the surgical intensive care unit since then. Her temperature is now rising and her chest radiograph reveals a new infiltrate in the right lower lobe. Her medical history includes coronary artery disease with a myocardial infarction 2 years ago, COPD, and hypertension. All antipseudomonal antibiotics in the institution are active against at least 90% of strains. B.P. has no known drug allergies. Which is the best empiric therapy for B.P.?

    A. Ceftriaxone 2 g intravenously every 24 hours plus gentamicin 7 mg/kg intravenously every 24 hours plus linezolid 600 mg intravenously every 12 hours.

    B. Piperacillin/tazobactam 4.5 g intravenously every 6 hours.

    C. Levofloxacin 750 mg intravenously every 24 hours plus linezolid 600 mg intravenously every 12 hours.

    D. Cefepime 2 g intravenously every 8 hours plus tobramycin 7 mg/kg intravenously every 24 hours plus vancomycin 15 mg/kg intravenously every 12 hours.

3. HAP
    a. Empiric regimen should include antibiotics with activity against *S. aureus* (MSSA), *P. aeruginosa*, and other gram-negative organisms.
    b. Options for single agents: Piperacillin/tazobactam, cefepime, levofloxacin, imipenem, or meropenem
    c. Two antibiotics with activity against *P. aeruginosa* should be included if the patient has received antibiotics in the past 90 days, has a high risk of mortality (indicated by the need for ventilator support or septic shock due to HAP), or for patients with structural lung disease (bronchiectasis or cystic fibrosis).
        i. Options for first agent: Antipseudomonal β-lactam (ceftazidime, cefepime, imipenem, meropenem, piperacillin/tazobactam, or aztreonam)
        ii. Options for second agent: Aminoglycoside, fluoroquinolone (ciprofloxacin, levofloxacin), or polymyxin (aztreonam may be used with another β-lactam if no other second option is available)
        iii. Aminoglycosides should not be used as monotherapy.
        iv. Aminoglycosides and polymyxins should be considered for both intravenous and inhaled delivery.

d. An antibiotic with activity against MRSA should be included if the patient has risk factors for MDR organisms, if MRSA incidence in the hospital unit is greater than 20%, or if the patient is at a high mortality risk.
    i. Options if MRSA activity necessary: Vancomycin or linezolid
    ii. Use oxacillin, nafcillin, or cefazolin for proven MSSA infections.
e. Ideally, dose antibiotics according to pharmacokinetic/pharmacodynamic data, including antibiotic serum concentrations, extended infusions of β-lactams, and weight-based dosing of aminoglycosides. See statement in HAP section regarding MRSA nasal screening.
f. Antibiotics should be de-escalated according to culture results. Antibiotic therapy for *P. aeruginosa* can be de-escalated to one active agent on the basis of culture and sensitivity results. Antibiotic therapy for MRSA can be de-escalated/discontinued on the basis of nasal PCR for MRSA results.
g. Treatment duration: A 7-day course is recommended for most infections
h. Antibiotics should be de-escalated on the basis of culture results. Antibiotic therapy for *P. aeruginosa* can be de-escalated to one active agent on the basis of culture and sensitivity results. Antibiotic therapy for MRSA can be de-escalated/discontinued on the basis of nasal PCR for MRSA results.

4. VAP
    a. Empiric regimen should include antibiotics with activity against *S. aureus* (MSSA), *P. aeruginosa*, and other gram-negative organisms.
    b. Options for single agents: Piperacillin/tazobactam, cefepime, levofloxacin, imipenem, or meropenem
    c. Two antibiotics with activity against *P. aeruginosa* should be included if the patient has risk factors for MDR organisms (see below), if *P. aeruginosa* resistance in the hospital unit to the antibiotic considered for monotherapy is greater than 10%, or for patients with structural lung disease (bronchiectasis or cystic fibrosis).
        i. Options for first agent: Antipseudomonal β-lactam (ceftazidime, cefepime, imipenem, meropenem, piperacillin/tazobactam, or aztreonam)
        ii. Options for second agent: Aminoglycoside, fluoroquinolone (ciprofloxacin, levofloxacin) or polymyxin (aztreonam may be used with another β-lactam if no other second option is available)
    d. Risk factors for MDR organisms
        i. Intravenous antibiotic therapy within the past 90 days
        ii. Hospitalization of 5 days or more prior to VAP
        iii. Septic shock at time of VAP
        iv. Acute respiratory distress syndrome preceding VAP
        v. Acute renal replacement therapy before VAP
    e. An antibiotic with activity against MRSA should be included if the patient has risk factors for MDR organisms (see above) or if MRSA incidence in the hospital unit is greater than 20%. Note: In locations where the prevalence of MRSA respiratory infections is low (< 10%), a negative MRSA nasal screen suggests that MRSA antibiotics are unnecessary empirically. Locations with a high prevalence of MRSA respiratory infections should follow the rule above.
        i. Options if MRSA activity necessary: Vancomycin or linezolid
    f. Ideally, dose antibiotics based on pharmacokinetic/pharmacodynamic data, including antibiotic serum concentrations, extended infusions of β-lactams and weight-based dosing of aminoglycosides
    g. Treatment duration: 7-day course is recommended for most infections.

F. Antibiotic Resistance
   1. Innate resistance – Based on characteristics of the microorganism (e.g., *P. aeruginosa* has innate resistance to vancomycin)
   2. Acquired resistance
      a. Mutations
      b. Horizontal gene transfer
   3. Mechanisms of resistance
      a. Decreased uptake (e.g., porins)
         i. β-Lactams
         ii. Fluoroquinolones
         iii. Aminoglycosides (especially *Pseudomonas*)
      b. Enzyme modification and degradation
         i. β-Lactamases (see Table 3)
         ii. Aminoglycoside hydrolytic enzymes (e.g., acetyltransferase, phosphotransferase, adenyl transferase) – Enteric gram-negative bacteria
      c. Altered target site
         i. β-Lactams (e.g., altered penicillin-binding proteins (PBPs), *mecA*) – *Staphylococcus*, *Streptococcus*, and *Enterococcus*
         ii. Glycopeptides (e.g., *vanA* and *vanB*) – Vancomycin resistance in *Enterococcus*
         iii. Fluoroquinolones (e.g., *gyrA* and *parC* mutations)
         iv. Ribosomal mutations (e.g., macrolides, tetracyclines)
         v. Sulfonamides (e.g., altered genes encoding dihydropteroate synthase)
         vi. Trimethoprim (e.g., altered genes encoding dihydrofolate reductase or overproduction of dihydrofolate reductase)
      d. Increased excretion (e.g., efflux pumps)
         i. Macrolides
         ii. Carbapenems
         iii. Fluoroquinolones
         iv. Tetracyclines

Table 3. β-Lactamases

Molecular Class	Category Name	Target	Examples	Effective Inhibitors
A	Serine β-lactamases	Penicillins, cephalosporins, aztreonam, carbapenems	CARB; TEM family; SHV family; CTX-M family; most ESBLs; CRE (KPC)	Avibactam, relebactam, vaborbactam ±clavulanic acid, ±sulbactam, ±tazobactam
B	Metallo β-lactamases	Carbapenems	IMP family, VIM family; CRE (NDM-1)	None
C	Serine β-lactamases	Cephalosporins	Amp C	Avibactam, relebactam, vaborbactam
D	Serine β-lactamases	Extended-spectrum cephalosporins, carbapenems	CRE (OXA family)	Avibactam

CARB = carbenicillin-hydrolysing β-lactamases; CRE = carbapenem-resistant Enterobacteriaceae; CTX-M = cefotaximase, Munich; ESBL = extended-spectrum β-lactamase; IMP = imipenemase; KPC = *Klebsiella pneumoniae* carbapenemase; NDM = New Delhi metallo-β-lactamase; OXA = oxacillinase; VIM = Verona integron-encoded metallo-β-lactamase.

G. Influenza
   1. Characteristics of influenza infection
      a. Epidemic with significant mortality
      b. Epidemics begin abruptly → peak in 2–3 weeks → resolve in 5–6 weeks.
      c. Occurs almost exclusively in the winter
      d. Average overall prevalence of 10%–20%
      e. Mortality greatest in those older than 65 years, with 80% of influenza-related deaths attributed to this age group. Patients with heart and lung disease are at the highest risk.
   2. Is it influenza, COVID-19, or the common cold? (Table 4)

Table 4. Differentiating the Symptoms of Influenza, COVID-19, and the Common Cold

Signs and Symptoms	Influenza	COVID-19	Common Cold
Onset	Sudden	Gradual	Gradual
Temperature	Characteristic, high (> 101°F [38°C]) of 3–4 days' duration	Common, but not consistently present	Occasional
Cough	Dry; can become severe	Dry with mucus; can become severe	Hacking
Headache	Prominent	Occasional	Occasional
Myalgia (muscle aches and pains)	Usual; often severe	Usual; can be severe	Slight
Tiredness and weakness	Can last 2–3 weeks	Can last 2–3 weeks	Very mild
Extreme exhaustion	Early and prominent	Common	Never
Chest discomfort	Common	Common	Mild to moderate
Stuffy nose	Sometimes	Common (especially with recent variants)	Common
Sneezing	Sometimes	Common (especially with recent variants)	Usual
Sore throat	Sometimes	Common (especially with recent variants)	Common
Loss of taste/smell	Never	Common	Never

   3. Pathophysiology
      a. Type A
         i. Influenza further grouped by variations in hemagglutinin and neuraminidase (e.g., H1N1, H3N2)
         ii. Changes through antigenic drift or shift
            (a) Drift: Annual, gradual change caused by mutations, substitutions, and deletions
            (b) Shift: Less common dramatic change leading to pandemics
         iii. Causes epidemics every 1–3 years
      b. Type B
         i. Type B influenza carries one form of hemagglutinin and one form of neuraminidase, both of which are less likely to mutate than the hemagglutinin and neuraminidase of type A influenza.
         ii. Changes through antigenic drift (minor mutations from year to year); when enough drifts occur, an epidemic is likely.
         iii. Causes epidemics every 5 years

4. Therapy
    a. Treatment with neuraminidase inhibitors indicated in patients with confirmed or suspected influenza and the following conditions:
        i. Hospitalized patients
        ii. Outpatients with severe or progressive illness
        iii. Outpatients at high risk of influenza complications
            (a) Patients younger than 2 years or 65 years and older
            (b) Patients with chronic disease states: Pulmonary (including asthma), cardiovascular (except hypertension alone), renal, hepatic, hematologic (including sickle cell disease), metabolic disorders (including diabetes), or neurologic and neurodevelopment conditions
            (c) Immunosuppressed patients
            (d) Pregnant women and those within 2 weeks postpartum
            (e) Patients younger than 19 years who are receiving long-term aspirin therapy
            (f) American Indians, Alaska Natives, non-Hispanic Black persons, and Hispanic or Latino persons
            (g) Patients who are morbidly obese
            (h) Residents of nursing homes and other long-term care facilities
        iv. Treatment may be considered for those without risk factors including:
            (a) Outpatients with illness onset less than 48 hours
            (b) Symptomatic outpatients who are household contacts of individuals at high risk of complications
            (c) Symptomatic health care providers who are caregivers for individuals at high risk of complications.
    b. Neuraminidase inhibitors
        i. Oseltamivir, zanamivir, peramivir
        ii. Inhibit neuraminidase; symptoms resolve 1–1.5 days sooner
        iii. Adverse effects
            (a) Oseltamivir: Gastrointestinal (GI) (nausea and vomiting), central nervous system (CNS) (anxiety, headache, insomnia, etc.)
            (b) Zanamivir: Bronchospasm, cough (not recommended in patients with asthma or COPD)
            (c) Peramivir: Diarrhea; and elevation of aspartate aminotransferase, alanine aminotransferase, creatinine phosphokinase, glucose
        iv. Dosage
            (a) Oseltamivir: 75 mg orally twice daily for 5 days; decrease dosage to 30 mg twice daily orally in patients with a creatinine clearance (CrCl) of 31–60 mL/minute/1.73 m^2 and 30 mg once daily orally in patients with a CrCl of 11–30 mL/minute/1.73 m^2.
            (b) Zanamivir: Two inhalations (5 mg/inhalation) twice daily for 5 days
            (c) Peramivir: 600 mg intravenously once; decrease dose to 200 and 100 mg in patients with a CrCl less than 50 and 30 mL/minute/1.73 m^2, respectively
            (d) Initiate within 48 hours of symptom onset.
    c. Endonuclease inhibitors
        i. Baloxavir
        ii. Inhibits viral endonuclease which is vital for initiating viral transcription; symptoms resolve 1-1.5 days sooner
        iii. Adverse effects: gastrointestinal, bronchitis, headache (all similar to placebo)
        iv. Dosage: 40 mg orally once (40-79 kg) or 80 mg orally once (greater than or equal to 80 kg)

5. Prevention
    a. Prophylaxis in the community
        i. Patients at very high risk of developing complications when influenza vaccination is contraindicated or for whom the vaccine is expected to have low effectiveness. Use for the duration of influenza activity.
        ii. Hematopoietic stem cell or lung transplant receipients, pending time since transplantation and degree of immunosuppression. Use for the duration of influenza activity.
        iii. Patients at high risk of complications or people in close contact with these patients. Use short term and give vaccine.
    b. Prophylaxis for institutional outbreaks
        i. All exposed residents or patients in outbreak-affected units regardless of influenza vaccination history
        ii. Unvaccinated or recently vaccinated caregivers
        iii. Use prophylaxis for at least 14 days and continue for 7 days after the last identified case in the institution.
    c. Oseltamivir 75 mg/day orally, baloxavir 40 mg once (less than 80 kg) or 80 mg once (greater than or equal to 80 kg) orally, zanamivir 10 mg/day inhaled

H. Coronavirus disease (COVID-19)
1. Characteristics of COVID-19 infection
    a. Caused by the SARS-CoV-2 virus
    b. Pandemic with significant mortality
    c. Occurs throughout the year
    d. Transmitted by exposure to respiratory fluids
    e. Incubation period of 3–6 days
    e. Mortality greatest in adults older than 65 years and in those with chronic conditions
2. Therapy
    a. Symptomatic/not hospitalized/not receiving supplemental oxygen
        i. Ritonavir-boosted nirmatrelvir (Paxlovid) is preferred first-line therapy as of January 2023
            (a) Dose: Nirmatrelvir 300 mg with ritonavir 100 mg orally twice daily for 5 days
            (b) Monitor patient closely for drug interactions
            (c) Dose reduction is recommended in patients with an eGFR of 30–59 mL/minute/1.73m^2.
        ii. Remdesivir is preferred second-line therapy (see dose below)
        iii. Molnupiravir is an alternative therapy if preferred therapies are not available/appropriate
    b. Hospitalized/receiving supplemental oxygen
        i. Remdesivir
            (a) Dose: 200 mg once; then 100 mg daily for total of 5 days
            (b) Benefit greatest when given early in disease course (within 10 days of symptom onset)
        ii. Dexamethasone
            (a) Dose: 6 mg orally or intravenously daily for 10 days; data also support doses of 20 mg daily for 5 days followed by 10 mg daily for 5 days and 12 mg daily for 10 days
            (b) Do not continue after discharge unless patient is still receiving supplemental oxygen
        iii. In patients with rapidly increasing oxygen needs and systemic inflammation, consider adding an immunomodulatory drug: baricitinib, tofacitinib, tocilizumab, sarilumab

Patient Case

3. S.C. is a 46-year-old woman who presents to the clinic with purulent nasal discharge, nasal and facial congestion, headaches, fever, and dental pain. Her symptoms began about 10 days ago, improved after about 4 days, and then worsened again a few days later. Which is the best empiric therapy for S.C.?
   A. Cefpodoxime proxetil 200 mg orally twice daily.
   B. Clindamycin 300 mg orally four times daily.
   C. Amoxicillin/clavulanate 875 mg/125 mg orally twice daily.
   D. No antibiotic therapy needed.

I. Sinusitis
   1. Definition and etiology
      a. Inflammation of the mucosal lining of the nasal passage and paranasal sinuses lasting up to 4 weeks
      b. Many different causes, including viruses, bacteria, and fungi
      c. Viruses account for more than 90% of cases, whereas bacteria account for less than 10%.
   2. Diagnosis
      a. Presence of at least two major symptoms or one major and two or more minor symptoms (Table 5)

Table 5. Symptoms Associated with Diagnosis of Sinusitis

Major Symptoms	Minor Symptoms
Purulent anterior nasal discharge	Headache
Purulent or discolored posterior nasal discharge	Ear pain, pressure, or fullness
Nasal congestion or obstruction	Halitosis
Facial congestion or fullness	Dental pain
Facial pain or pressure	Cough
Hyposmia or anosmia	Fever (for subacute or chronic sinusitis)
Fever (for acute sinusitis only)	Fatigue

      b. Viral or bacterial? (Table 6)

Table 6. Differentiating Viral from Bacterial Sinusitis

Characteristics	Viral	Bacterial
Symptoms	Nasal discharge, congestion, and scratchy throat	Nasal discharge, congestion, and scratchy throat
Nasal discharge	Clear to purulent to clear; purulence not present until days 4–5	Persistent purulent discharge (> 10 days) *or* early and severe (first 3–4 days) *or* increased on days 5–6 after typical viral infection ("double-sickening")
Fever	None (or early in course, resolving in 48 hr)	High temperature (≥ 102.2°F [39°C]) and early (first 3–4 days)
Other symptoms	Headache, facial pain, and myalgia (resolving in 48 hr)	Headache, facial pain, myalgia, daytime cough
Peak symptoms	Days 3–6	Persistent > 10 days *or* early and severe (first 3–4 days) *or* improved symptoms that worsen on days 5–6
Duration	5–10 days	In general, > 10 days

3. Treatment
    a. Begin antibiotics as soon as *bacterial* sinusitis is diagnosed (see criteria in Table 6).
    b. First-line therapy
        i. Amoxicillin/clavulanate
        ii. High-dose amoxicillin/clavulanate (2 g/125 mg twice daily in adults or 90/6.435 mg/kg/day divided twice daily) in:
            (a) Geographic regions with high endemic rates (greater than 10%) of invasive penicillin-nonsusceptible *S. pneumoniae*
            (b) Those with a severe infection (e.g., evidence of systemic toxicity with a temperature of 102.2°F (39°C) or higher and a threat of suppurative complications)
            (c) Attendance at day care
            (d) Age younger than 2 years or older than 65 years
            (e) Recent hospitalization
            (f) Antibiotic use within the past month
            (g) Those who are immunocompromised
    c. Second-line therapy
        i. Doxycycline
        ii. Cefixime or cefpodoxime proxetil with clindamycin (for children with non–type I hypersensitivity to penicillin)
        iii. Respiratory fluoroquinolone (including children with type I hypersensitivity to penicillin) - Because of serious adverse effects, avoid if there are other treatment options.
        iv. Intranasal saline irrigation as adjunctive therapy
        v. Intranasal corticosteroids as adjunctive therapy in patients with allergic rhinitis
    d. Therapy duration
        i. Adults: 5–7 days
        ii. Children: 10–14 days

II. URINARY TRACT INFECTIONS

A. Introduction
1. Most common bacterial infection in humans: 7 million office visits per year; 1 million hospitalizations
2. Many women (15%–20%) will have a urinary tract infection (UTI) during their lifetime
3. 1–50 years of age: UTIs occur predominantly in women; after 50: men are increasingly affected because of prostate problems

B. Microbiology (Table 7)

Table 7. Incidence of Urinary Tract Infections by Organism

Community Acquired (%)		**Nosocomial (%)**	
Escherichia coli	73	*E. coli*	31
Staphylococcus saprophyticus	13	*Pseudomonas aeruginosa*	10
Proteus mirabilis	5	Other gram-negative bacilli	10
Klebsiella pneumoniae	4	*K. pneumoniae*	9
Enterococcus	2	*Staphylococcus aureus*	6
		P. mirabilis	5
		Enterococcus	2

C. Predisposing Factors
   1. Age
   2. Female sex
   3. Diabetes
   4. Pregnancy
   5. Immunosuppression
   6. Urinary tract instrumentation
   7. Urinary tract obstruction
   8. Renal disease, renal transplantation
   9. Neurologic dysfunction

Patient Case

4. G.N. is a 62-year-old woman who presents to the emergency department with a 3-day history of urinary frequency and dysuria. During the past 24 hours, she has had nausea, vomiting, and flank pain. G.N. has a history of type 2 diabetes, which is poorly controlled, with some diabetes-related complications. G.N. also has hypertension and a history of several episodes of deep venous thrombosis. Her medications include glyburide 5 mg orally daily, enalapril 10 mg orally twice daily, warfarin 3 mg orally daily, and metoclopramide 10 mg orally four times daily. On physical examination, she is alert and oriented, with the following vital signs: temperature 102.8°F (39°C), heart rate 120 beats/minute, respiratory rate 16 breaths/minute, supine blood pressure 140/75 mm Hg, and standing blood pressure 110/60 mm Hg. Her laboratory values are within normal limits except for elevated international normalized ratio 2.7, BUN 26 mg/dL, SCr 1.88 mg/dL, and WBC 12,000 cells/mm^3 (78 polymorphonuclear leukocytes, 7 band neutrophils, 10 lymphocytes, and 5 monocytes). Her urinalysis reveals turbidity, 2+ glucose, pH 7.0, protein 100 mg/dL, 50–100 WBCs, positive nitrites, 3–5 red blood cells, and many bacteria and positive for casts. Which is the best empiric therapy for G.N.?

   A. Trimethoprim/sulfamethoxazole double strength orally twice daily for 7 days. Monitor INR carefully.

   B. Ciprofloxacin 400 mg intravenously twice daily and then 500 mg orally twice daily for a total of 7 days. Monitor INR carefully.

   C. Gentamicin 140 mg intravenously every 24 hours for 3 days.

   D. Tigecycline 100 mg once, then 50 mg intravenously every 12 hours and then doxycycline 100 mg orally twice daily for a total of 10 days.

D. Clinical Presentation
   1. Lower UTI: Cystitis (older adults may have only nonspecific symptoms, such as mental status changes, abdominal pain, and decreased eating or drinking)
      a. Dysuria
      b. Frequent urination
      c. Urgency
      d. Occasionally, gross hematuria
   2. Upper UTI: Pyelonephritis (older adults may have only nonspecific symptoms, such as mental status changes, abdominal pain, and decreased eating or drinking)
      a. Frequency, dysuria, hematuria
      b. Suprapubic pain
      c. Costovertebral angle tenderness; flank pain
      d. Fever, chills
      e. Elevated WBC
      f. Nausea, vomiting

3. Factors associated with or used to define complicated UTI (UTI involving a structural or functional abnormality)
    a. Male sex
    b. Hospital acquired
    c. Pregnancy
    d. Anatomic abnormality of the urinary tract
    e. Poorly controlled diabetes
    f. Recent antimicrobial use
    g. Indwelling urinary catheter
    h. Recent urinary tract instrumentation
    i. Immunosuppression
4. Recurrent cystitis
    a. Relapse: Infection with the same organism within 14 days of discontinuing antibiotics for the preceding UTI
    b. Reinfection: Infection with a completely different organism; most common cause of recurrent cystitis

E. Diagnosis: Urinalysis (blood cultures will be positive in 20% of patients with upper UTIs)
1. Pyuria (WBC greater than 10 cells/mm^3)
2. Bacteriuria (more than 10^2 colony-forming units per milliliter is diagnostic) in symptomatic patients or those with catheters
3. Red blood cells
4. Cloudiness
5. Nitrite positive (*E. coli, Proteus, Klebsiella*)
6. Leukocyte esterase positive
7. Casts (if pyelonephritis)
8. Note: patient must also have symptoms; diagnosis cannot be made on urinalysis results alone.

F. Asymptomatic Bacteriuria
1. Asymptomatic bacteriuria should only be screened for and treated in pregnant women, patients undergoing endoscopic urologic procedures, and renal transplant recipients in the first 30 days after transplantation.
    a. Pregnant women should be treated for 4–7 days.
    b. Patients undergoing endoscopic urologic procedures should be treated with one or two doses of antibiotics.
2. Patients with functional and/or cognitive impairment should not be treated for asymptomatic bacteriuria solely on the basis of a history of falls or mental status changes/confusion. Patients must have local urinary symptoms or systemic signs of infection.

G. Therapy
1. Uncomplicated cystitis
    a. Recommended therapy
        i. Trimethoprim/sulfamethoxazole 160 mg/800 mg twice daily for 3 days. Avoid if resistance prevalence is known to exceed 20% or if used for UTI in previous 3 months.
        ii. Nitrofurantoin monohydrate/macrocrystals 100 mg twice daily for 5 days (ineffective in patients with a CrCl less than 30 mL/minute/1.73 m^2)
        iii. Fosfomycin tromethamine 3 g, one dose
    b. Alternatives
        i. β-Lactams (amoxicillin-clavulanate, cefdinir, cefaclor, cephalexin, and cefpodoxime proxetil) for 5–7 days

ii. Fluoroquinolones (not moxifloxacin) for 3 days – Because of serious adverse effects, avoid fluoroquinolones if there are other treatment options.

2. Uncomplicated pyelonephritis
   a. Outpatient therapy (if patient is not immunocompromised or does not have nausea and vomiting)
      i. Trimethoprim/sulfamethoxazole 160 mg/800 mg twice daily for 14 days
      ii. Levofloxacin 750 mg orally daily for 5 days or ciprofloxacin 500 mg orally twice daily for 7 days – Because of serious adverse effects, avoid fluoroquinolones if there are other treatment options.
      iii. β-Lactams (see above) for 10–14 days (less effective than first two options)
   b. Uropathogen resistance greater than 10%: Use initial dose of an intravenous, long-acting β-lactam (e.g., ceftriaxone) or once-daily aminoglycoside.
3. Complicated UTIs
   a. Outpatient therapy
      i. Trimethoprim/sulfamethoxazole 160 mg/800 mg twice daily for 7-14 days
      ii. Levofloxacin 750mg oral daily for 5 days or ciprofloxacin 500mg oral twice daily for 7 days – Because of serious adverse effects, avoid fluoroquinolones if there are other treatment options.
      iii. β-Lactams (see above) for 7–14 days (less effective than first two options)
   b. Inpatient therapy
      i. Ceftriaxone (consider a β-lactam with antipseudomonal activity in patients recently hospitalized or with urinary catheters or living in nursing homes)
      ii. Fluoroquinolone
      iii. Aminoglycoside
      iv. Therapy duration: 5–14 days (5 days with levofloxacin)
4. Pregnancy (pregnant women should be screened for bacteriuria and treated, even if asymptomatic)
   a. Antibiotic options
      i. Amoxicillin/clavulanate for 3-7 days
      ii. Nitrofurantoin (avoid in the first trimester and at term if other options available) for 5-7 days
      iii. Cephalexin or cefpodoxime proxetil for 3-7 days
      iv. Fosfomycin tromethamine single dose
   b. Antibiotics to avoid
      i. Fluoroquinolones
      ii. Tetracyclines
      iii. Aminoglycosides
      iv. Trimethoprim/sulfamethoxazole (used frequently but avoidance recommended, especially during the late third trimester)
5. Recurrent cystitis
   a. Relapse
      i. Assess for pharmacologic reason for treatment failure.
      ii. Longer treatment (for 2 weeks, depending on length of initial course)
   b. Reinfection (reassess need for continuous prophylactic antibiotics every 6–12 months)
      i. If patient has two or fewer UTIs in 1 year, use patient-initiated therapy for symptomatic episodes (3-day treatment regimens).
      ii. If patient has three or more UTIs in 1 year and they are temporally related to sexual activity, use postintercourse prophylaxis with trimethoprim/sulfamethoxazole single strength, cephalexin 250 mg, or nitrofurantoin 50 mg and counsel on voiding after intercourse.
      iii. If patient has three or more UTIs in 1 year that are not related to sexual activity, use daily or three times per week prophylaxis with trimethoprim 100 mg, trimethoprim/sulfamethoxazole single strength, cephalexin 250 mg, or nitrofurantoin 50 mg.

6. Catheter-related UTIs
    a. Short-term indwelling catheters
        i. Risk of bacteriuria is 5% for each day of catheterization.
        ii. By 30 days, 75%–95% of patients with an indwelling catheter will have bacteriuria.
        iii. Preventive antimicrobial therapy is not recommended; it only increases the chance of selecting out resistant organisms.
        iv. Asymptomatic patients with bacteriuria should not be treated.
        v. Symptomatic patients with bacteriuria should be treated with 7 days of antibiotics if symptoms resolve promptly and with 10–14 days of antibiotics if there is a delayed response (both durations whether or not catheter removed). Treat for 5 days with levofloxacin if the patient is not severely ill; treat for 3 days in women 65 years and younger who have their catheters removed and who do not have upper urinary tract symptoms.
        vi. The most common organisms are *E. coli* (21.4%), *Enterococcus* spp. (14.9%), *P. aeruginosa* (10.0%), *K. pneumoniae* (7.7%), and *Enterobacter* spp. (4.1%).
    b. Long-term indwelling catheters
        i. Almost all patients will be bacteriuric with two to five organisms.
        ii. Asymptomatic patients should not be treated. Catheters do not need to be replaced.
        iii. Symptomatic patients should be treated for a short period (7 days) to prevent resistance, and catheter replacement may be indicated.
7. Prostatitis
    a. Acute bacterial prostatitis
        i. Primarily gram-negative organisms
        ii. Therapy duration 2–4 weeks, can extend for an additional 2 weeks if patient remains symptomatic
            (a) Trimethoprim/sulfamethoxazole
            (b) Fluoroquinolones
    b. Chronic bacterial prostatitis
        i. Difficult to treat
        ii. Therapy duration 1–4 months
            (a) Trimethoprim/sulfamethoxazole
            (b) Fluoroquinolones
8. Epididymitis
    a. Sexually transmitted (most likely caused by *C. trachomatis* or *N. gonorrhoeae*)
        i. Ceftriaxone 500 mg (1000 mg if weight greater than 150 kg) intramuscularly once plus doxycycline 100 mg twice daily
        ii. Use levofloxacin 500 mg daily instead of doxycycline in men who practice insertive anal sex.
        iii. Duration: 10 days
    b. Non-sexually transmitted (most likely caused by enteric gram-negative organisms):
        i. Men with bladder outlet obstruction (benign prostatic hyperplasia) or who have undergone prostate biopsy, vasectomy, or other urinary tract instrumentation procedures
        ii. Levofloxacin 500 mg daily
        iii. Duration: 10 days

III. SKIN AND SKIN STRUCTURE INFECTIONS

A. Cellulitis
   1. Description
      a. Acute spreading skin infection that involves primarily the deep dermis and subcutaneous fat
      b. Nonelevated, poorly defined margins
      c. Warmth, pain, generalized erythema and edema, and tender lymphadenopathy
      d. Malaise, fever, and chills
      e. Usually, patient has had previous minor trauma, abrasions, ulcers, or surgery (could be tinea infections, psoriasis, or eczema).
      f. Often, patients have impaired lymphatic drainage.
   2. Microorganism: Usually *Streptococcus pyogenes* and occasionally *S. aureus* (rarely other organisms); blood cultures are rarely positive and not routinely recommended unless severe systemic symptoms are present or the patient is immunosuppressed
   3. Treatment: 5–10 days (may extend therapy if infection has not improved)
      a. Penicillin G if definitively streptococcal
      b. First-generation cephalosporin (cefazolin, cephalexin)
      c. Ceftriaxone
      d. Clindamycin (resistance can be observed)
      e. Treat empirically for MRSA if associated with penetrating trauma, injection drug use, purulent drainage, nasal colonization with MRSA, concurrent evidence of MRSA infection elsewhere or systemic inflammatory response syndrome (SIRS) criteria (severe nonpurulent).
         i. Outpatient: Clindamycin, trimethoprim/sulfamethoxazole (add β-lactam for *Streptococcus*), doxycycline (add β-lactam for *Streptococcus*)
         ii. Inpatient: Vancomycin, linezolid, daptomycin, or telavancin

B. Erysipelas
   1. Description
      a. Acute spreading skin infection that involves primarily the superficial dermis
      b. Spreads rapidly through the lymphatic system in the skin (patients may have impaired lymphatic drainage)
      c. Usually occurs in infants and older adults
      d. Usually occurs on the legs and feet (facial erysipelas can occur, but this is less common)
      e. Warmth, erythema, and pain
      f. Edge of infection is elevated and sharply demarcated from the surrounding tissue.
      g. Systemic signs of infection are common, but blood cultures are positive only 5% of the time.
   2. Microorganism: Group A *Streptococcus* (*S. pyogenes*), but occasionally groups G, C, and B are seen
   3. Treatment: 5 days (may extend therapy if infection has not improved)
      a. Penicillin G
      b. Cefazolin
      c. Clindamycin (resistance can be observed)

C. Necrotizing Fasciitis
   1. Description
      a. Acute, necrotizing cellulitis that involves the subcutaneous fat and superficial fascia
      b. Infection extensively alters surrounding tissue, leading to cutaneous anesthesia or gangrene.
      c. Very painful (pain out of proportion to appearance)
      d. Streptococcal infection: Either spontaneous or attributable to varicella, minor trauma (cuts, burns, and splinters), or surgical procedures

e. Mixed infection: generally secondary to perianal abscess, abdominal surgery, trauma, decubitus ulcers, or injection sites in persons who inject drugs
f. Significant systemic symptoms, including shock and organ failure

2. Microorganisms
   a. Mixed infection with facultative and anaerobic bacteria (Type 1)
   b. *S. pyogenes* (Type 2)
3. Treatment
   a. Surgical debridement: Most important therapy and often repeated debridement is necessary
   b. Antibiotics are not curative; given in addition to surgery (if used early, may be effective alone)
   c. Empiric therapy: Vancomycin or linezolid plus piperacillin/tazobactam or a carbapenem or ceftriaxone with metronidazole
      i. If group A streptococci, *S. aureus*, or *Clostridium* spp. suspected, clindamycin or linezolid should be included in the empiric regimen to suppress toxin and cytokine production
   d. Streptococcal necrotizing fasciitis: High-dose intravenous penicillin plus clindamycin or linezolid clindamycin

D. Varicella
1. Description
   a. Maculopapules, vesicles, and scabs in varying stages
   b. Lesions initially contain clear vesicular fluid before they pustulate and scab
   c. Typically appear on the trunk and face before spreading to other areas of the body
2. Microorganism
   a. Varicella-Zoster virus
3. Treatment
   a. Acyclovir 800 mg orally 4–5 times daily for 5 days
   b. Valacyclovir 1 g orally three times daily for 5–7 days

Patient Case

5. G.N. returns to the clinic in 6 months with no urinary symptoms, but her chief concern is now an ulcer on her right foot. She recently returned from a vacation in Florida and thinks she might have stepped on something while walking barefoot on the beach. Her foot is not sore but is red and swollen around the deep ulcer. Her medications are the same as in Patient Case 4. Vital signs are stable, and there is nothing significant on physical examination except for the right foot ulcer. Laboratory values are within normal limits (SCr 0.86 mg/dL). Which is the best empiric therapy for G.N.?

   A. Nafcillin 2 g intravenously every 6 hours for 6–12 weeks.

   B. Tobramycin 120 mg intravenously every 12 hours plus levofloxacin 750 mg intravenously every 24 hours for 1–2 weeks.

   C. Piperacillin/tazobactam 3.375 g intravenously every 6 hours for 1–2 weeks.

   D. Below-the-knee amputation followed by ceftriaxone 1 g intravenously every 24 hours for 1 week.

IV. DIABETIC FOOT INFECTIONS

A. Epidemiology
1. 25% of people with diabetes develop foot infections.
2. 1 in 15 needs amputation.

B. Etiology
   1. Neuropathy: Motor and autonomic
      a. Mechanical or thermal injuries lead to ulcerations without patient knowledge.
      b. Gait disturbances and foot deformities; maldistribution of weight on the foot
      c. Diminished sweating, causing dry, cracked skin
   2. Vasculopathy: Decreased lower limb perfusion
   3. Immunologic defects: Cellular and humoral

C. Causative Organisms: In general, polymicrobial (average, 2.1–5.8 microorganisms)
   1. *S. aureus*
   2. Group A and B *Streptococcus*
   3. *Enterococcus*
   4. *Proteus*
   5. *E. coli*
   6. *Klebsiella*
   7. *Enterobacter*
   8. *P. aeruginosa*
   9. *Bacteroides fragilis*
   10. *Peptostreptococcus*

D. Therapy
   1. Preventive therapy
      a. Examine feet daily for calluses, blisters, trauma, and so forth.
      b. Wear properly fitting shoes.
      c. Do not walk barefoot.
      d. Keep feet clean and dry.
      e. Have toenails cut properly.
   2. Antimicrobial therapy
      a. Mild infections (and no antibiotics in the past month), defined as local infection involving only the skin and the subcutaneous tissue, with no SIRS criteria and erythema of 2 cm or less
         i. No MRSA risk factors: Dicloxacillin, nafcillin, oxacillin, cephalexin, cefazolin, levofloxacin, doxycycline, trimethoprim/sulfamethoxazole (in case of β-lactam allergy), moxifloxacin, or clindamycin
         ii. High risk for MRSA (previous MRSA infection or colonization): Linezolid, clindamycin (resistance can be observed), doxycycline, or trimethoprim/sulfamethoxazole
      b. Moderate to severe infections, defined as local infection with erythema greater than 2 cm, or involving structures deeper than skin and subcutaneous tissues without (moderate) or with (severe) 2 or more SIRS criteria
         i. Ampicillin/sulbactam
         ii. Second or third generation cephalosporin (e.g., cefuroxime, cefotaxime, ceftriaxone)
         iii. If recent antibiotics, piperacillin/tazobactam, second or third generation cephalosporins, or ertapenem.
         iv. If macerated ulcer or warm climate, use piperacillin/tazobactam, dicloxacillin or nafcillin or oxacillin with ceftazidime or ciprofloxacin, or meropenem or imipenem
         v. If ischemic limb/necrosis/gas-forming, use amoxicillin/clavulanate, ampicillin/sulbactam, or piperacillin/tazobactam
         vi. If risk for resistant gram-negative organisms, use ertapenem, meropenem, imipenem, ciprofloxacin, aminoglycoside, or polymyxin.

vii. If risk of MRSA, use vancomycin, linezolid, doxycycline, trimethoprim/sulfamethoxazole, or daptomycin. Risk factors for MRSA include prolonged hospitalization, intensive care unit admission, recent hospitalization, recent antibiotic use, invasive procedure, HIV infection, admission to nursing homes, open wounds, hemodialysis, and discharge with long-term central venous access.

c. Treatment duration: 1–2 weeks, consider continuing treatment for up to 3–4 weeks in patients with extensive infection and slow response and/or underlying history of severe PAD. Six weeks is needed for osteomyelitis. After amputation, treatment duration is 2–5 days if there is no remaining infected tissue or or bone, 1–2 weeks if residual infected tissue only, 3 weeks if residual infected bone, and 6 weeks if no surgery or dead bone.

E. Surgical Therapy
   1. Drainage and debridement (appropriate wound care) are very important.
   2. Amputation is often necessary; if infection is discovered early, can maintain structural integrity of the foot.

Patient Case

6. W.A. is a 55-year-old man who is admitted with weight loss, malaise, and severe back pain and spasms that have progressed during the past 2 months. He has also experienced loss of sensation in his lower extremities. Four months before this admission, he had surgery for a fractured tibia, followed by an infection treated with unknown antibiotics. W.A. has hypertension and a history of diverticulitis. On physical examination, he is alert and oriented, with the following vital signs: temperature 99.4°F (37.4°C), heart rate 88 beats/minute, respiratory rate 14 breaths/minute, and blood pressure 130/85 mm Hg. His laboratory values are within normal limits, except for WBC 14,300 cells/mm^3, erythrocyte sedimentation rate 89 mm/hour, and C-reactive protein 12 mg/dL. Magnetic resonance imaging reveals bony destruction of lumbar vertebrae 1 and 2, which is confirmed by a bone scan. A computed tomography–guided bone biopsy reveals gram-positive cocci in clusters. Which is the best therapy for W.A.?

   A. Vancomycin 15 mg/kg intravenously every 12 hours for 6 weeks.

   B. Nafcillin 2 g intravenously every 6 hours for 2 weeks.

   C. Levofloxacin 750 mg orally every 24 hours for 6 weeks.

   D. Ampicillin/sulbactam 3 g intravenously every 6 hours for 2 weeks.

V. OSTEOMYELITIS

A. Introduction
   1. Infection of the bone with subsequent bone destruction
   2. About 20 cases per 100,000 people

B. Characteristics (Table 8)

Table 8. Characteristics of Osteomyelitis

	Hematogenous Spread	Contiguous Spread	Vascular Insufficiency
Definition	Spread of bacteria through the bloodstream from a distant site	Spread of bacteria from an adjacent tissue infection or by direct inoculation	Infection results from insufficient blood supply to fight the bacteria
Patient population	Children (< 16 yr): femur, tibia, humerus Adult: vertebrae	Adults (25–50 yr): femur, tibia, skull	Adults (> 50 yr)
Predisposing factors	Bacteremia (e.g., IV catheters, PWID, skin infections, URI) Sickle cell anemia	Open reduction of fractures Gunshot wound Dental or sinus infections Soft tissue infections	Diabetes PVD Post-CABG (sternum)
Common pathogens	Usually monomicrobial Children: *Staphylococcus aureus* (60%–90%), *Staphylococcus epidermidis*, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Enterobacter*, *Escherichia coli* (all < 5%) Adults: *S. aureus* and gram-negative bacilli Sickle cell anemia: *Salmonella* (67%), *S. aureus, S. pneumoniae* PWID: *P. aeruginosa*	Usually mixed infection: *S. aureus* (60%), *S. epidermidis, Streptococcus* Gram-negative bacilli: *P. aeruginosa* (foot punctures), *Proteus*, *Klebsiella*, *E. coli* Anaerobic (human bites, decubitus ulcers)	Usually polymicrobial: *S. aureus, S. epidermidis, Streptococcus* Gram-negative bacilli Anaerobic (*Bacteroides fragilis* group) Infected prosthesis: *S. aureus, S. epidermidis*

CABG = coronary artery bypass graft; IV = intravenous; PVD = peripheral vascular disease; PWID = patients who inject drugs; URI = upper respiratory infection; yr = year.

C. Clinical Presentation
   1. Signs and symptoms
      a. Fever and chills
      b. Localized pain, tenderness, and swelling
      c. Neurologic symptoms if spinal cord compression
   2. Laboratory tests
      a. Elevated WBC
      b. Elevated erythrocyte sedimentation rate
      c. Elevated C-reactive protein
   3. Diagnostic tests
      a. Radiographic tests: Positive results lag behind infectious process.
      b. Computed tomography and magnetic resonance imaging scans
      c. Radionuclide imaging: Positive as soon as 24–48 hours after infectious process begins.

D. Empiric Therapy
   1. Pediatric (neonate therapy should be tailored to the patient)
      a. Cefazolin
      b. Nafcillin, oxacillin
      c. Clindamycin (use if prevalence of MRSA in community is 10% or more)
      d. Vancomycin (use if prevalence of MRSA and clindamycin-resistant *S. aureus* in community is 10% or more)

2. Adults
    a. Empiric therapy often includes gram-negative coverage (e.g., cefazolin, ceftriaxone, cefepime, meropenem) combined with an anti-staphylococcal agent (e.g., clindamycin, doxycycline, vancomycin, linezolid, or daptomycin).
    b. Choose additional antibiotics according to patient-specific characteristics.
3. Patients with sickle cell anemia: Ceftriaxone/cefotaxime or ciprofloxacin/levofloxacin (no studies assessing best empiric therapy). Patients are at risk of *Salmonella*.
4. Prosthetic joint infections
    a. Debridement and retention of prosthesis or one-stage exchange of prosthesis
        i. Staphylococcal: Pathogen-specific intravenous therapy plus rifampin 300–450 mg twice daily for 2–6 weeks, followed by rifampin plus ciprofloxacin or levofloxacin for 3 months (hip, elbow, shoulder, ankle prosthesis) or 6 months (retained knee prosthesis)
        ii. Nonstaphylococcal: Pathogen-specific intravenous (or highly bioavailable oral) therapy for 4–6 weeks, followed by indefinite oral suppression therapy
    b. Resection of prosthesis with or without planned reimplantation or amputation
        i. Pathogen-specific intravenous (or highly bioavailable oral) therapy for 4–6 weeks
        ii. Only 24–48 hours of antibiotic therapy after amputation if all infected tissue is removed
    c. Following a 1-stage joint exchange (which is uncommon in the United States), indefinite oral suppressive therapy may be considered.

E. Therapy Length
1. Acute osteomyelitis: 3–6 weeks (average 6 weeks)
2. Chronic osteomyelitis: 6–8 weeks of parenteral and/or highly bioavailable oral therapy; duration may be extended for patients perceived to be at high risk of failure (e.g., MRSA, extensive infection)

F. Criteria for Effective Oral Therapy for Osteomyelitis
1. Highly bioavailable antibiotic is available.
2. Adherence
3. Identified organism that is highly susceptible to the oral antibiotic used
4. C-reactive protein less than 2.0 mg/dL
5. Adequate surgical debridement
6. Resolving clinical course

VI. CENTRAL NERVOUS SYSTEM INFECTIONS

A. Meningitis: Introduction
1. Incidence: About 8.6 cases per 100,000 people
2. Occurs more often in male than in female patients
3. More common in children

B. Microbiology (Table 9)
   1. Bacterial (septic meningitis)

Table 9. Bacterial Etiology of Meningitis, Based on Age

Age	Most Likely Organisms	Less Common Organisms
< 1 mo (newborns)	*Streptococcus agalactiae* *Listeria monocytogenes* *Streptococcus pneumoniae* *Neisseria meningitidis*	*Escherichia coli*, *Klebsiella* spp. Herpes simplex type 2
1–23 mo	*Streptococcus pneumoniae* *Neisseria meningitidis* *Haemophilus influenzae* *Streptococcus agalactiae*	Viruses *E. coli*
2–50 yr	*N. meningitidis* *S. pneumoniae*	*H. influenzae* Viruses
> 50 yr	*S. pneumoniae* *N. meningitidis* *L. monocytogenes*	*Streptococcus agalactiae*, *H. influenzae*, aerobic gram-negative bacilli, viruses

   2. Other causes (aseptic meningitis)
      a. Viral
      b. Fungal
      c. Parasitic
      d. Tubercular
      e. Syphilis
      f. Drugs (e.g., trimethoprim/sulfamethoxazole, ibuprofen)

C. Predisposing Factors
   1. Head trauma
   2. Immunosuppression
   3. CNS shunts
   4. Cerebrospinal fluid (CSF) fistula or leak
   5. Neurosurgical patients
   6. Alcoholism
   7. Local infections
      a. Sinusitis
      b. Otitis media
      c. Pharyngitis
      d. Bacterial pneumonia
   8. Splenectomized patients
   9. Sickle cell disease
   10. Congenital defects

D. Clinical Presentation
   1. Symptoms
      a. Fever, chills
      b. Headache, backache, nuchal rigidity, mental status changes, photophobia
      c. Nausea, vomiting, anorexia, poor feeding habits (infants)
      d. Petechiae or purpura (*N. meningitidis* meningitis)

2. Physical signs
    a. Brudzinski sign
    b. Kernig sign
    c. Bulging fontanel (infants only)

E. Diagnosis
1. History and physical examination
2. Blood cultures
3. Lumbar puncture
    a. Elevated opening pressure
    b. Composition in bacterial meningitis (Table 10)

Table 10. CSF Changes in Bacterial Meningitis

Component	Normal CSF	Bacterial Meningitis	Viral Meningitis
Glucose	30–70 mg/dL (2/3 peripheral)	< 50 mg/dL (≤ 0.4 CSF:blood)	Normal
Protein	< 50 mg/dL	> 150 mg/dL	Normal to slightly elevated
WBC	< 5 cells/mm^3	> 1000–5000 cells/mm^3 (predominantly neutrophils)	5–300 cells/mm^3 (predominantly lymphocytes)
pH	7.3	7.1	7.3
Lactic acid	< 14 mg/dL	> 35 mg/dL	< 14 mg/dL

CSF = cerebrospinal fluid.

    c. CSF stains and studies
        i. Gram stain (microorganisms): Helps identify organism in 60%–90% of cases
        ii. Latex agglutination: High sensitivity, 50%–100%, for common organisms
            (a) Not recommended routinely
            (b) Most useful in patients pretreated with antibiotics with subsequent negative CSF Gram stains and cultures
        iii. Polymerase chain reaction (PCR): Detects most common causes of bacterial meningitis; high specificity and sensitivity
        iv. Acid-fast staining (tubercular meningitis)
        v. Cryptococcal antigen
        vi. Herpes simplex virus PCR
4. Laboratory findings
    a. Elevated WBC with a left shift
    b. CSF Gram stain
    c. CSF cultures (positive in 75%–80% of bacterial meningitis cases)
    d. Blood cultures (±)
    e. C-reactive protein concentrations: High negative predictive value

Patient Case

7. D.M. is a 21-year-old university student who presents to the emergency department with the worst headache of his life. During the past few days, he has felt slightly ill but has been able to go to class regularly and eat and drink adequately. This morning, he awoke with a terrible headache and pain whenever he moved his neck. He has no significant medical history and takes no medications. He cannot remember the last time he received a vaccination. On physical examination, he is in extreme pain (10/10) with the following vital signs: temperature 102.4°F (39.1°C), heart rate 110 beats/minute, respiratory rate 18 breaths/minute, and blood pressure 130/75 mm Hg. His laboratory values are within normal limits, except for WBC 22,500 cells/mm^3 (82 polymorphonuclear leukocytes, 11 band neutrophils, 5 lymphocytes, and 2 monocytes). A computed tomography scan of the head is normal, so a lumbar puncture is performed with the following results: glucose 44 mg/dL (peripheral, 110), protein 220 mg/dL, and WBC 800 cells/mm^3 (85% neutrophils, 15% lymphocytes). Which is the best empiric therapy for D.M.?

   A. Penicillin G 4 million units intravenously every 4 hours.

   B. Ceftriaxone 2 g intravenously every 12 hours.

   C. Ceftriaxone 2 g intravenously every 12 hours plus dexamethasone 10 mg intravenously every 6 hours.

   D. Ceftriaxone 2 g intravenously every 12 hours plus vancomycin 1000 mg intravenously every 8 hours plus dexamethasone 10 mg intravenously every 6 hours.

F. Empiric Therapy
   1. Neonates (less than 1 month)
      a. Ampicillin plus aminoglycoside *or*
      b. Ampicillin plus cefotaxime
   2. Infants (1–23 months): Ceftriaxone plus vancomycin*
   3. Children and adults (2–50 years): Ceftriaxone plus vancomycin*
   4. Older adults (50 years and older): Ceftriaxone plus vancomycin* plus ampicillin
   5. Penetrating head trauma, neurosurgery, or CSF shunt: Vancomycin plus cefepime, ceftazidime, or meropenem

      *Vancomycin added for activity against highly drug-resistant *S. pneumoniae*.

G. Therapy for Common Pathogens
   1. *S. pneumoniae*
      a. An MIC to penicillin of 0.1 mcg/mL or less
         i. Penicillin G 4 million units intravenously every 4 hours
         ii. Ampicillin 2 g intravenously every 4 hours
         iii. Alternative: Ceftriaxone 2 g intravenously every 12 hours or chloramphenicol 1–1.5 g intravenously every 6 hours
      b. An MIC to penicillin of 0.1–1.0 mcg/mL
         i. Ceftriaxone
         ii. Alternative: Cefepime 2 g intravenously every 8 hours or meropenem 2 g intravenously every 8 hours
      c. An MIC to penicillin of 2.0 mcg/mL or greater
         i. Vancomycin 15–20 mg/kg intravenously every 8–12 hours plus ceftriaxone
         ii. Alternative: Moxifloxacin 400 mg intravenously every 24 hours
         iii. If cephalosporin resistant: Vancomycin plus rifampin, vancomycin plus ceftriaxone or cefotaxime, rifampin plus ceftriaxone or cefotaxime, vancomycin plus moxifloxacin, linezolid

2. *N. meningitidis*
    a. An MIC to penicillin of less than 0.1 mcg/mL
        i. Penicillin G
        ii. Ampicillin
        iii. Alternative: Third-generation cephalosporin (cefotaxime or ceftriaxone) or chloramphenicol
    b. An MIC 0.1–1.0 mcg/mL
        i. Ceftriaxone
        ii. Alternative: Chloramphenicol, fluoroquinolone, or meropenem
3. *H. influenzae*
    a. β-Lactamase negative
        i. Ampicillin
        ii. Alternative: Third-generation cephalosporin (cefotaxime or ceftriaxone), cefepime, chloramphenicol, or fluoroquinolone
    b. β-Lactamase positive
        i. Third-generation cephalosporin (cefotaxime or ceftriaxone)
        ii. Alternative: Cefepime, chloramphenicol, or fluoroquinolone
4. *Streptococcus agalactiae*
    a. Penicillin G
    b. Ampicillin
    c. Alternative: Third-generation cephalosporin (cefotaxime or ceftriaxone)
5. *Listeria monocytogenes*
    a. Penicillin G
    b. Ampicillin
    c. Alternative: Trimethoprim/sulfamethoxazole 5 mg/kg intravenously every 6–12 hours or meropenem
6. Herpes simplex virus
    a. Intravenous acyclovir 10 mg/kg/dose every 8 hours infused over 1 hour
    b. Drug resistance: cidofovir or foscarnet

H. Therapy Length: Based on clinical experience, not on clinical data
1. *N. meningitidis:* 7 days
2. *H. influenzae:* 7 days
3. *S. pneumoniae:* 10–14 days
4. *S. agalactiae*: 14–21 days
5. *Listeria monocytogenes*: 21 days or more
6. Herpes simplex: 10–14 days (meningitis), 14–21 days (encephalitis)

I. Adjunctive Corticosteroid Therapy
1. Risks and benefits
    a. Significantly less hearing loss and other neurologic sequelae in children receiving dexamethasone for *H. influenzae* meningitis
    b. Significantly improved outcomes, including decreased mortality, in adults receiving dexamethasone for *S. pneumoniae* meningitis
    c. May decrease antibiotic penetration (decreased penetration of vancomycin in animals after dexamethasone)
2. Dosage and administration
    a. Give corticosteroids 10–20 minutes before or at same time as first dose of antibiotics.
    b. Dexamethasone 0.15 mg/kg or 10 mg every 6 hours for 2–4 days
    c. Use in children with *H. influenzae* meningitis or in adults with pneumococcal meningitis; however, may need to initiate before knowing specific causative bacteria.

Patient Case

8. D.M.'s CSF cultures grew *N. meningitidis*. Which is the best recommendation for meningitis prophylaxis?
   A. The health care providers in close contact with D.M. should receive rifampin 600 mg orally every 12 hours for four doses.
   B. Everyone in D.M.'s dormitory and in all of his classes should receive rifampin 600 mg orally every 24 hours for 4 days.
   C. Everyone in the emergency department at the time of D.M.'s presentation should receive the meningococcal conjugate vaccine.
   D. Everyone in the emergency department at the time of D.M.'s presentation should receive rifampin 600 mg orally every 12 hours for four doses.

J. Chemoprophylaxis
   1. *N. meningitidis*
      For close contacts (household or day care) and exposure to oral secretions of index case
      a. Rifampin
         i. Adults: 600 mg every 12 hours, four doses
         ii. Children: 10 mg/kg every 12 hours, four doses (max 600 mg/dose)
         iii. Infants (younger than 1 month): 5 mg/kg every 12 hours, four doses
      b. Ciprofloxacin 500 mg orally, one dose (adults only)
      c. Ceftriaxone 125–250 mg intramuscularly, one dose
   2. *H. influenzae*
      For all close contacts in households with unvaccinated or immunocompromised children
      a. Adults: Rifampin 600 mg daily for 4 days
      b. Children (1 month to 12 years): Rifampin 20 mg/kg/day for 4 days (max 600 mg/dose)
      c. Infants younger than 1 month: Rifampin 10 mg/kg/day for 4 days

K. Brain Abscess
   1. Pathophysiology
      a. Direct extension or retrograde septic phlebitis from otitis media, mastoiditis, sinusitis, and facial cellulitis
      b. Hematogenous: Particularly lung abscess or infective endocarditis: 3%–20% have no detectable focus.
   2. Signs and symptoms
      a. Expanding intracranial mass lesion: Focal neurologic deficits
      b. Headache
      c. Fever
      d. Seizures
      e. Mortality is about 50%.
   3. Microbiology
      a. Usually polymicrobial
      b. *Streptococcus* spp. in 50%–60%
      c. Anaerobes in about 40%
   4. Therapy
      a. Incision and drainage: By craniotomy or stereotaxic needle aspiration
      b. Suggested empiric regimens based on source of infection
         i. Otitis media or mastoiditis: Metronidazole plus ceftriaxone
         ii. Sinusitis: Metronidazole plus ceftriaxone

iii. Dental sepsis: Penicillin plus metronidazole
iv. Trauma or neurosurgery: Vancomycin plus cefepime
v. Lung abscess, empyema: Penicillin plus metronidazole plus sulfonamide
vi. Unknown: Vancomycin plus metronidazole plus ceftriaxone

c. Corticosteroids if elevated intracranial pressure

Patient Case

9. T.S. is a 48-year-old man who presents to the emergency department with fever, chills, nausea and vomiting, anorexia, lymphangitis in his right hand, and lower back pain. He has no significant medical history except for kidney stones 4 years ago. He has no known drug allergies. He is homeless and was a person with substance use disorder (intravenous heroin) for the past year but quit 2 weeks ago. On physical examination, he is alert and oriented, with the following vital signs: temperature 100.8°F (38°C), heart rate 114 beats/minute, respiratory rate 12 breaths/minute, and blood pressure 127/78 mm Hg. He has a faint systolic ejection murmur, and his right hand is erythematous and swollen. His laboratory values are all within normal limits. He had an HIV test 1 year ago, which was negative. One blood culture was obtained in the emergency department that later grew MSSA. Two more cultures were obtained 24 hours after the first culture and are now both growing gram-positive cocci in clusters. A transesophageal echocardiogram reveals vegetation on the mitral valve. Which is the best therapeutic regimen for T.S.?

A. Nafcillin therapy for 7–10 days.
B. Nafcillin plus rifampin plus gentamicin therapy for 6 weeks or longer.
C. Nafcillin plus gentamicin therapy for 2 weeks of both antibiotics.
D. Nafcillin therapy for 6 weeks.

VII. ENDOCARDITIS

A. Introduction
1. Infection of the heart valves or other endocardial tissue
2. Platelet-fibrin complex becomes infected with microorganisms: Vegetation
3. Main risk factors include mitral valve prolapse, prosthetic valves, and persons who inject drugs (PWID).
4. 13.8 cases per 100,000 people per year

B. Presentation and Clinical Findings
1. Signs and symptoms
a. Fever: Low grade and remittent
b. Cutaneous manifestations (50% of patients): Petechiae (including conjunctival), Janeway lesions, splinter hemorrhage
c. Cardiac murmur (90% of patients)
d. Arthralgias, myalgias, low back pain, arthritis
e. Fatigue, anorexia, weight loss, night sweats
2. Laboratory findings
a. Anemia: Normochromic, normocytic
b. Leukocytosis
c. Elevated erythrocyte sedimentation rate and C-reactive protein
d. Positive blood culture in 78%–95% of patients

3. Complications
    a. Congestive heart failure: 38%–60% of patients
    b. Emboli: 22%–43% of patients
    c. Mycotic aneurysm: 5%–10% of patients

C. Microbiology (Table 11)

Table 11. Incidence of Microorganisms in Endocarditis

Organism	Incidence (%)
Streptococcus	50
Staphylococcus aureus	25
Enterococcus	8
Coagulase-negative *Staphylococcus*	7
Gram-negative bacilli	6
Candida albicans	2

D. Treatment (Table 12)

Table 12. Treatment Recommendation for Endocarditis

Organism	Recommended Therapy	Length of Therapy (wk)	
		Native Valve	Prosthetic Valve
PCN-susceptible oral streptococci and *S. gallolyticus* group	PCN G	4	6
	PCN G + gentamicin[a]	2	6[b]
	Amoxicillin	2	6[b]
	Ceftriaxone	4	6
	Ceftriaxone + gentamicin	2	6[b]
	Vancomycin (only if unable to tolerate PCN or ceftriaxone)	4	6
Oral streptococci and *S. gallolyticus* group susceptible, increased exposure, or resistant to PCN	PCN G + gentamicin	4[c]	6[d]
	Amoxicillin + gentamicin	4	6
	Ceftriaxone + gentamicin	4	6[d]
	Vancomycin (only if unable to tolerate PCN or ceftriaxone)	4	6
Staphylococcus, methicillin sensitive	Oxacillin or nafcillin Plus gentamicin and rifampin in prosthetic valves	6	≥ 6[c]
	Cefazolin Plus gentamicin and rifampin in prosthetic valves	6	≥ 6[c]
	Daptomycin (only if severe PCN allergy) Plus gentamicin and rifampin or ceftaroline in prosthetic valves	6	≥ 6[c]

Table 12. Treatment Recommendation for Endocarditis *(Cont'd)*

Organism	Recommended Therapy	Length of Therapy (wk)	
		Native Valve	Prosthetic Valve
Staphylococcus, methicillin resistant	Vancomycin Plus rifampin and gentamicin in prosthetic valves	6	≥ 6[c]
	Daptomycin (not for prosthetic valves) ± ceftaroline	6	—
Enterococcus	Ampicillin + gentamicin	4–6	6
	Ampicillin + ceftriaxone	6	6
	Vancomycin + gentamicin (only if unable to tolerate a β-lactam)	6	6
Enterococcus, β-lactam resistant	Vancomycin + gentamicin	6	6
Enterococcus, PCN, aminoglycoside, and vancomycin resistant	Daptomycin + ampicillin, ertapenem, or ceftaroline	> 6	> 6
HACEK group	Ceftriaxone	4	6
	Ampicillin + gentamicin[e]	4	6
	Fluoroquinolone (ciprofloxacin, levofloxacin, moxifloxacin)	4	6

[a]Gentamicin should preferably be given as a single daily dose (3 mg/kg) for viridans streptococci endocarditis but may be given daily in three equally divided doses as an alternative.

[b]Gentamicin can be added for 2 wk if CrCl is greater than 30 mL/minute/1.73 m^2.

[c]Gentamicin for 2 wk.

[d]Gentamicin for 6 wk.

[e]Gentamicin should be for 2 weeks, and this option can be considered in patients with β-lactamase negative strains.

HACEK = *Haemophilus*, *Aggregatibacter*, *Cardiobacterium*, *Eikenella*, *Kingella*; MIC = minimum inhibitory concentration; PCN = penicillin.

E. Prophylaxis (Table 13)

Table 13. Endocarditis Prophylaxis

Conditions in Which Prophylaxis Is Necessary	Dental Procedures That Require Prophylaxis
Prosthetic cardiac valves including bioprosthetic and homograft valves Previous bacterial endocarditis Congenital heart disease	Any dental procedure that involves the gingival tissues or periapical region of a tooth and for procedures that perforate the oral mucosa
Cyanotic congenital heart disease Repaired congenital heart defect with prosthetic material or device, during the first 6 months after the procedure or lifelong if residual shunt Cardiac transplant recipients who develop cardiac valvulopathy Patients with ventricular assist devices May consider in heart transplant recipients	**Other Procedures That Require Prophylaxis** Invasive diagnostic or therapeutic procedures of the respiratory, gastrointestinal, genitourinary tract, skin, or musculoskeletal systems in high-risk patients

F. Recommended Prophylaxis for Dental or Respiratory Tract Procedures (Table 14)

Table 14. Prophylaxis for Dental or Respiratory Tract Procedures

Situation	Agent	Regimen
Standard general prophylaxis	Amoxicillin	Adults: 2 g; children: 50 mg/kg 1 hr before procedure
Unable to take oral medications	Ampicillin	Adults: 2 g IM/IV; children: 50 mg/kg IM/IV within 30 min before procedure
	Cefazolin or ceftriaxone	Adults: 1 g IM/IV; children: 50 mg/kg IM/IV within 30 minutes before procedure
Allergy to penicillin	Cephalexin	Adults: 2 g; children: 50 mg/kg 1 hr before procedure
	Azithromycin or clarithromycin	Adults: 500 mg; children: 15 mg/kg 1 hr before procedure
	Doxycycline	Adults: 100 mg; children: 2.2 mg/kg (<45 kg), 100 mg (>45 kg)
	Cefazolin or ceftriaxone	Adults: 1 g IM/IV; children: 50 mg/kg IM/IV
Allergic to penicillin and unable to take oral medications	Cefazolin or ceftriaxone	Adults: 1 g IM/IV; children: 50 mg/kg IM/IV within 30 min before procedure

IM = intramuscularly; IV = intravenously.

Patient Case

10. Six months after treatment of his endocarditis, T.S. is visiting his dentist for a tooth extraction. Which antibiotic is best for prophylaxis?
    A. Tooth extractions do not warrant endocarditis prophylaxis.
    B. Administer amoxicillin 2 g 1 hour before the extraction.
    C. Administer amoxicillin 3 g 1 hour before the extraction and 1.5 g every 6 hours for four doses after the extraction.
    D. T.S. is not at increased risk of endocarditis and does not need prophylactic antibiotics.

VIII. PERITONITIS AND INTRA-ABDOMINAL INFECTIONS

A. Introduction
   1. Definition: Inflammation of the peritoneum (serous membrane lining the abdominal cavity)
   2. Types
      a. Primary: Spontaneous or idiopathic, no primary focus of infection
      b. Secondary: Occurs secondary to an abdominal process

B. Primary Peritonitis: Spontaneous Bacterial Peritonitis (see the "Gastrointestinal Disorders" chapter)

C. Secondary Peritonitis
   1. Etiology:
      a. Peptic ulcer perforation
      b. Perforation of a GI organ
      c. Appendicitis
      d. Endometritis secondary to intrauterine device

e. Bile peritonitis
f. Pancreatitis
g. Operative contamination
h. Diverticulitis/colitis
i. Intestinal neoplasms
j. Secondary to peritoneal dialysis

2. Microbiology of intra-abdominal infections
   a. Stomach and proximal small intestine: Aerobic and facultative gram-positive and gram-negative organisms
   b. Ileum: *E. coli, Enterococcus,* anaerobes
   c. Large intestine: Obligate anaerobes (i.e., *Bacteroides, Clostridium perfringens*), aerobic and facultative gram-positive and gram-negative organisms (i.e., *E. coli, Streptococcus, Enterococcus, Klebsiella, Proteus, Enterobacter*)
3. Clinical manifestations and diagnosis
   a. Fever, tachycardia
   b. Elevated WBC
   c. Abdominal pain aggravated by motion, rebound tenderness
   d. Bowel paralysis
   e. Pain with breathing
   f. Decreased renal perfusion
   g. Ascitic fluid
      i. Protein: High (more than 3 g/dL); exudate fluid
      ii. WBCs: Many, primarily granulocytes

D. Therapy: Secondary Peritonitis
1. Therapy or prophylaxis should be limited in
   a. Bowel injuries caused by trauma that are repaired within 12 hours (treat for less than 24 hours)
   b. Intraoperative contamination by enteric contents (treat for less than 24 hours)
   c. Perforations of the stomach, duodenum, and proximal jejunum (unless patient is on antacid therapy or has malignancy) (prophylactic antibiotics for less than 24 hours)
   d. Acute appendicitis without evidence of perforation, abscess, or peritonitis (treat for less than 24 hours)
2. Mild to moderate community-acquired infection
   a. Cefoxitin
   b. Cefazolin, cefuroxime, or ceftriaxone, plus metronidazole
   c. Ertapenem
   d. Moxifloxacin
   e. Ciprofloxacin plus metronidazole or levofloxacin plus metronidazole
   f. Tigecycline
3. High-risk or severe* community-acquired or health care–acquired infection (*High-risk or severe is defined as APACHE II score greater than 15, advanced age, poor nutritional status/low albumin concentration, comorbidities and organ dysfunction, an inability to achieve adequate source control, presence of malignancy, severe physiologic disturbance, or immunosuppression.)
   a. Piperacillin/tazobactam
   b. Ceftazidime or cefepime, plus metronidazole
   c. Imipenem/cilastatin or meropenem
   d. Ciprofloxacin plus metronidazole or levofloxacin plus metronidazole (not for health care–acquired infections)

e. Consider adding an aminoglycoside when extended-spectrum β-lactamase–producing Enterobacterales or drug-resistant *P. aeruginosa* is of concern (healthcare-acquired infections only and when greater than 20% of *P. aeruginosa* isolates are ceftazidime resistant)
f. Consider adding vancomycin for MRSA if colonized with MRSA or prior treatment failure with extensive antibiotic exposure (health care–acquired infections only)
g. Add antifungal therapy if *Candida* spp. grown from intra-abdominal cultures
h. Consider using antibiotics effective against *Enterococcus* (especially if patient has received cephalosporins, has valvular disease, is immunocompromised or post-operative)

4. Therapy duration: 4 days following source control

IX. *CLOSTRIDIOIDES DIFFICILE* INFECTION

Patient Case

11. R.K. is a 72-year-old man who presents to the emergency department with a 2-day history of redness and swelling of his upper right extremity. He scraped his arm while clearing some brush in his yard. Although the scratch was initially healing, the area around the injury has become red and warm to the touch over the past few days, and the redness appears to be spreading. His medical history includes gastroesophageal reflux disease, hypertension, hyperlipidemia, and osteoarthritis. R.K. is taking pantoprazole 40 mg orally daily, lisinopril 20 mg orally daily, atorvastatin 40 mg orally daily, and acetaminophen 500 mg orally as needed. R.K. has no known drug allergies. R.K. is hospitalized and sent home after a few days with a prescription for oral clindamycin for his cellulitis. Two weeks after completing therapy for his cellulitis, R.K. has watery diarrhea. R.K. goes to the emergency department, and his *C. difficile* toxin is positive. His WBC is 24,500 cells/mm^3, albumin is 2.8 g/dL, and SCr is 1.74 mg/dL (normally around 0.90 mg/dL). Which is the best therapeutic regimen for R.K.?

A. Metronidazole 500 mg orally three times daily for 7 days.
B. Vancomycin 125 mg orally four times daily for 10 days.
C. Fidaxomicin 200 mg orally twice daily for 14 days.
D. Rifaximin 400 mg orally twice daily for 7 days.

A. Introduction
1. *Clostridioides difficile* is transmitted by the fecal-oral route.
2. Overgrowth in the GI tract occurs after antibiotic therapy.
3. Risk factors: Hospital stays, medical comorbidities (e.g., oncology, inflammatory bowel disease, chronic kidney disease, organ transplant), extremes of age, immunodeficiency states, use of broad-spectrum antibiotics, use of proton pump inhibitors
4. Production of endotoxins A and B causes pathogenesis.
5. Symptoms: Watery diarrhea, abdominal pain, leukocytosis, GI tract complications
6. Disease severity:
   a. Non-severe: Leukocytosis with WBC less than 15 x 10^3 cells/mm^3 and SCr 1.5 mg/dL or less
   b. Severe: Leukocytosis with WBC 15 x 10^3 cells/mm^3 or greater or SCr greater than 1.5 mg/dL
   c. Fulminant: Hypotension or shock or ileus or megacolon
7. BI/NAP1 strain produces more enterotoxin, produces binary toxin, and has increased sporulation capacity. Increased risk of metronidazole failure, morbidity, and mortality

B. Therapy
   1. Initial episode
      a. Nonsevere infection
         i. Vancomycin 125 mg orally four times a day for 10 days
         ii. Fidaxomicin 200 mg orally twice daily for 10 days. No difference in clinical cure rates compared with vancomycin but lowered incidence of recurrence. IDSA guidelines conditionally suggest using first line over vancomycin.
         iii. Metronidazole (500 mg orally three times daily for 10 days) may be used for nonsevere infection if vancomycin and fidaxomicin are unavailable
      b. Severe infection
         i. Vancomycin 125 mg orally four times a day for 10 days
         ii. Fidaxomicin 200 mg orally twice daily for 10 days. IDSA guidelines conditionally suggest using first line over vancomycin.
      c. Fulminant infection: Vancomycin 500 mg orally four times daily for 10 days. Consider adding metronidazole 500 mg intravenously every 8 hours (especially in patients with ileus). In addition, in patients with ileus, add vancomycin per rectum 500 mg in 100 mL of saline as an enema four times daily. Can discontinue metronidazole and enemas if ileus resolves.
   2. First recurrence
      a. Following metronidazole: Vancomycin 125 mg orally four times daily for 10 days or fidaxomicin 200 mg orally twice daily for 10 days
      b. Following vancomycin:
         i. Vancomycin prolonged taper and pulsed dosing: 125 mg orally four times daily for 10-14 days, then twice daily for a week, then daily for a week then every 2-3 days for 2-8 weeks
         ii. Fidaxomicin 200 mg orally two times daily for 10 days. IDSA guidelines conditionally suggest using fidaxomicin over vancomycin standard or pulsed dosing for first recurrences.
      c. Following fidaxomicin: Vancomycin prolonged taper and pulsed dosing. IDSA guidelines conditionally suggest using fidaxomicin for first recurrences over vancomycin standard or pulsed dosing (even with recurrences after fidaxomicin therapy).
   3. Second and subsequent recurrences
      a. Fecal microbiota transplantation
      b. Fidaxomicin 200 mg orally twice daily for 10 days
      c. Vancomycin prolonged taper and pulsed dosing
      d. Vancomycin 125 mg orally four times daily for 10 days followed by rifaximin 400 mg three times daily for 20 days
      e. Fecal microbiota (Live; Rebyota) 150 mL rectally once 24–72 hours after vancomycin/fidaxomicin
      f. Fecal microbiota (Live; Vowst) 4 capsules orally every 24 hours for 3 days, 2–4 days after vancomycin/fidaxomicin
   4. Recurrence prevention
      a. Oral vancomycin prophylaxis
         i. Alternative in patients when fidaxomicin not an option/unsuccessful (up to 8 weeks)
         ii. Option in high-risk (older than 65 or immunocompromised with *C. difficile* infection (CDI) in past 3 months) patients needing systemic antibiotics (use during and for 5 days after antibiotic discontinuation)
         iii. Vancomycin 125 mg orally daily
      b. Bezlotoxumab
         i. Human monoclonal antibody that binds to *C. difficile* toxin B, preventing recurrent infections
         ii. Indicated in patients who are at high risk of recurrence (one or more prior episodes within the previous 6 months, older than 65, immunocompromised, or have clinically severe CDI at presentation)

iii. Dose: 10 mg/kg intravenously as a single 60-minute infusion given during standard antibiotic therapy (does not replace standard antibiotic therapy)
iv. Lower incidence of recurrent CDI infection in 12 weeks (17% vs. 27%)

Patient Case

12. You are a pharmacist who works closely with the surgery department to optimize therapy for patients undergoing surgical procedures at your institution. The surgeons provide you with principles of surgical prophylaxis that they believe are appropriate. Which is the best practice for optimizing surgical prophylaxis?
    A. Antibiotics should be redosed for extended surgical procedures; redose if the surgery lasts longer than 4 hours or involves considerable blood loss.
    B. All patients should be given antibiotics for 24 hours after the procedure; this will optimize prophylaxis.
    C. Preoperative antibiotics can be given up to 4 hours before the incision; this will make giving the antibiotics logistically easier.
    D. Vancomycin is the antibiotic of choice for surgical wound prophylaxis because of its long half-life and activity against MRSA.

X. SURGICAL PROPHYLAXIS

A. Introduction
    1. Prophylaxis: Administering the putative agent before bacterial contamination occurs
    2. Early therapy: Immediate or prompt institution of therapy as soon as the patient presents; usually, contamination or infection will have preceded the initiation of therapy (e.g., dirty wounds).
B. Classification of Surgical Procedures (Table 15)

Table 15. Classification of Surgical Procedures

Surgical Procedure	Infection Rate (%)
Clean: No entry is made in the respiratory, GI, or genitourinary tracts or in the oropharyngeal cavity In general, it is elective with no break in technique and no inflammation encountered	1–4
Clean contaminated: Entry in the respiratory, GI, genitourinary, or biliary tracts or oropharyngeal cavity without unusual contamination Includes clean procedures with a minor break in technique	5–15
Contaminated: Includes fresh traumatic wounds, gross spillage from the GI tract (without a mechanical bowel preparation), a major break in technique, or incisions encountering acute, nonpurulent inflammation	16–25
Dirty: Includes procedures involving old traumatic wounds, perforated viscera, or clinically evident infection	30–100

C. Risk Factors for Postoperative Wound Infections
    1. Bacterial contamination
        a. Exogenous sources: Flaw in aseptic technique
        b. Endogenous sources
            i. Most important except in clean procedures
            ii. Patient flora causes infection

2. Host resistance
    a. Extremes of age
    b. Nutrition (i.e., malnourished patients)
    c. Obesity
    d. Diabetes (decreased wound healing and increased risk of infection)
    e. Immunocompromised
    f. Hypoxemia
    g. Remote infection
    h. Presence of foreign body (healthy person tolerates inoculum of 10^5, but in the presence of a foreign body, only 10^2 are needed)

D. Indications for Surgical Prophylaxis
    1. Common postoperative infection with low morbidity
    2. Uncommon postoperative infection with significant morbidity and mortality

E. Principles of Prophylaxis (Figure 1)
    1. Timing: Antibiotics must be present in the tissues at the time of bacterial contamination (incision) and throughout the operative period; on-call dosing is not acceptable.
        a. Administering antibiotics earlier than immediately preoperatively (within 60 minutes before incision or 60–120 minutes if using vancomycin or a fluoroquinolone) is unnecessary.
        b. Initiating antibiotics postoperatively is no more effective than not administering prophylaxis.
        c. Redose if the surgery lasts longer than 4 hours (or more than 2 half-lives of the antibiotic) or involves considerable blood loss.

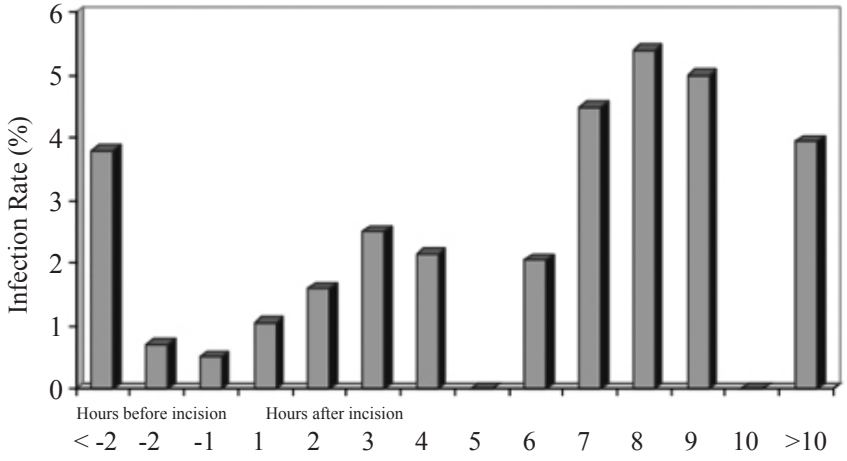


Figure 1. Relationship between timing of surgical prophylaxis and postoperative infection rate.

Data from: Classen DC, Evans RS, Pestotnik SL, et al. The timing of prophylactic administration of antibiotics and the risk of surgical-wound infection. N Engl J Med 1992;326:281-6.

2. Dosage
    a. Adequate dosing is necessary to prevent postoperative skin infections. Obese patients have a higher incidence of postoperative infections.
    b. Appropriate dosing
        i. Cefazolin: 2 g (3 g for patients weighing 120 kg or more)
        ii. Ceftriaxone and cefoxitin: 2 g
        iii. Clindamycin: 900 mg
        iv. Vancomycin: 15 mg/kg

3. Duration
    a. Most procedures, including GI, orthopedic, and gynecologic procedures, warrant antibiotics only as long as the patient is in the operating room; administration beyond surgical closure is not necessary.
    b. Cardiac procedures may warrant 24–48 hours of antibiotics after surgery.
4. Spectrum
    a. Need only activity against skin flora unless the operation violates a hollow viscus mucosa
    b. GI, genitourinary, hepatobiliary, and some pulmonary operations warrant additional antibiotics.
    c. Colorectal surgery is one procedure in which broad-spectrum aerobic and anaerobic coverage is most effective.
    d. Try to avoid a drug that may be needed for therapy if infection occurs.
5. Adverse reactions and bacterial resistance
    a. Antibiotic prophylaxis should not cause greater morbidity than the infection it prevents.
    b. Overuse may lead to resistance, which could prevent further use of the antibiotic for surgical prophylaxis or other infections (duration of administration is an important factor).
6. Cost
    a. Prophylaxis can account for a substantial portion of the antibiotic budget.
    b. Must be weighed against the cost of treating one person with a postoperative infection

F. Antibiotic Prophylaxis in Specific Surgical Procedures
Note: For patients colonized with MRSA, a single preoperative dose of vancomycin can be added.
1. GI
    a. Gastric or duodenal
        i. Because of acidity, little normal flora
        ii. Rates of intragastric organisms and postoperative infections increase with increasing pH.
        iii. Indicated for morbid obesity, esophageal obstruction, decreased gastric acidity, or decreased GI motility
        iv. Recommendation: Cefazolin 2 g before induction
    b. Biliary
        i. Biliary tract normally has no organisms.
        ii. Indicated for high-risk patients. (Often, intraoperative cholangiography reveals unexpected common duct stones, so some studies recommend using antibiotics in all biliary surgery. In addition, studies have shown an increase in infection rates without risk factors.)
            (a) Acute cholecystitis
            (b) Obstructive jaundice
            (c) Common duct stones
            (d) Age older than 70 years
        iii. Recommendation: Cefazolin, cefoxitin, or ceftriaxone 2 g or ampicillin/sulbactam 3 g before induction
    c. Appendectomy
        i. Acutely inflamed or normal appendix: Less than 10% risk
        ii. Evidence of perforation: More than 50% risk (treatment necessary)
        iii. If perforated appendix, treat for 4 days.
        iv. Recommendation: Cefoxitin 2 g (or cefazolin plus metronidazole or ertapenem 1 g) before induction
    d. Colorectal
        i. A 30%–77% infection rate without antibiotics
        ii. One of the few surgical procedures in which coverage for aerobes *and* anaerobes has proved most effective

iii. Preoperative antibiotics
(a) Combined oral and parenteral regimens result in lower rates of surgical wound infections, anastomotic leaks, 30-day mortality, and postoperative ileus.
(b) Oral regimens are inexpensive; however, some data suggest they are less effective when used alone (without parenteral agents), have greater toxicity, and may increase the risk of CDI.

e. Recommendation
i. Cefazolin or ceftriaxone 2 g plus metronidazole 500 mg (or cefoxitin 2 g or ampicillin/sulbactam 3 g or ertapenem 1 g or the combination of gentamicin/tobramycin 5 mg/kg plus either clindamycin 900 mg or metronidazole 500 mg) before induction
ii. With or without neomycin 1 g orally and erythromycin 1 g orally at 2:00 p.m., 3:00 p.m., and 10:00 p.m. the day before surgery or neomycin 1 g orally and metronidazole 500 mg orally at 2:00 p.m., 3:00 p.m., and 10:00 p.m. the day before surgery
iii. Mechanical bowel preparation is not recommended.

2. Obstetrics and gynecology
a. Vaginal or abdominal hysterectomy
i. Antibiotics are most effective in vaginal hysterectomies but generally are given for both procedures.
ii. Recommendation: Cefazolin or cefoxitin 2 g (or ampicillin/sulbactam 3 g) before induction
b. Cesarean section. Recommendation: Cefazolin 2 g prior to incision or as soon after the incision if an emergency surgery
i. Consider cefazolin 3 g in patients weighing greater than or equal to 120 kg
ii. Consider adding azithromycin 500 mg for women undergoing nonelective cesarean
c. For procedures lasting greater than two drug half-lives (greater than 4 hours for cefazolin from time of dose), administer an additional intraoperative dose of the same antibiotic

3. Cardiothoracic
a. Cardiac surgery
i. Antibiotics decrease the risk of mediastinitis.
ii. Recommendation: Cefazolin or cefuroxime 2 g preinduction (plus intraoperative doses), if MRSA is probable or patient has been hospitalized, use vancomycin
b. Pulmonary resection (i.e., lobectomy and pneumonectomy). Recommendation: Cefazolin 2 g before induction (or ampicillin/sulbactam 3 g or vancomycin 15 mg/kg)
c. Vascular surgery
i. High mortality with infected grafts
ii. Recommendation: Cefazolin 2 g before induction and every 8 hours for three doses; if MRSA is probable, use vancomycin

4. Orthopedic
a. Prophylaxis is indicated when surgery involves prosthetic materials (i.e., total hip or knee, nail, or plate).
b. Recommendation: Cefazolin 2 g before induction (or vancomycin)

5. Head and neck
a. Indicated for major surgical procedures when an incision is made through the oral or pharyngeal mucosa
b. Recommendation: Cefazolin or cefuroxime 2 g plus metronidazole 500 mg or ampicillin/sulbactam 3 g or clindamycin 900 mg before induction

6. Urologic
a. In general, not recommended for Class I and most Class II procedures. For Class III and Class IV procedures, can use either a single dose or less than 24 hours of parenteral antibiotics
b. Indicated if patient has a positive urine culture before surgery (should treat and then operate)
c. If therapy is unsuccessful, cover for the infecting organism and operate.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: C

Although ampicillin/sulbactam has good activity against *H. influenzae*, *Moraxella catarrhalis*, and *S. pneumoniae* (but not drug-resistant *S. pneumoniae* [DRSP]), it has no activity against atypical organisms (*L. pneumophila*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*). Current recommendations are to include a macrolide with a β-lactam antibiotic for hospitalized patients with CAP (Answer A is incorrect). Piperacillin/tazobactam has good activity against *H. influenzae*, *M. catarrhalis*, and *S. pneumoniae* (but not DRSP) and, with gentamicin, is excellent for pneumonia caused by most gram-negative organisms. However, this increased activity is not necessary for CAP, and the combination has no activity against atypical organisms (Answer B is incorrect). Ceftriaxone plus azithromycin is the best initial choice. It has excellent activity against atypical organisms (because of azithromycin), *H. influenzae*, *M. catarrhalis*, and *S. pneumoniae* (even intermediate DRSP) (Answer C is correct). Although doxycycline has activity against atypical organisms and most of the typical organisms that cause CAP, it is not recommended as monotherapy in hospitalized patients. In addition, its activity against *S. pneumoniae* may be limited (if the patient lives in an area with extensive DRSP). Doxycycline would not be the best initial choice (Answer D is incorrect).

2. Answer: D

Ceftriaxone plus gentamicin plus linezolid is not good empiric therapy because ceftriaxone has no activity against *P. aeruginosa*. Because the patient has been in a hospital for 5 days or more (8 days at this point), she is at increased risk of MDR organisms, specifically *P. aeruginosa* and MRSA (Answer A is incorrect). Although piperacillin/tazobactam has good activity against most common causes of nosocomial pneumonia (including *P. aeruginosa*), the most recent guidelines recommend two antibiotics with activity against *P. aeruginosa* for patients with risk factors for MDR organisms She also needs an antibiotic with MRSA activity (Answer B is incorrect). Levofloxacin has activity against *P. aeruginosa,* but two drugs should be used (Answer C is incorrect). Cefepime plus tobramycin plus vancomycin is the best empiric therapy because it includes two antibiotics with activity against *P. aeruginosa* and another agent for MRSA (Answer D is correct).

3. Answer: C

This patient has symptoms suggestive of bacterial sinusitis, including two major symptoms and a few minor symptoms. That the symptoms improved and then worsened suggests a bacterial sinusitis that followed a viral infection (Answer D is incorrect). Although the combination of cefpodoxime and clindamycin is an option for sinusitis in penicillin-allergic patients, it is not recommended to give either of these alone for treatment (Answers A and B are incorrect). The best option is amoxicillin/clavulanate, which has activity against organisms commonly seen in bacterial sinusitis and is considered a first-line agent (Answer C is correct).

4. Answer: B

While oral trimethoprim/sulfamethoxazole can be considered for pyelonephritis, it is not appropriate in this patient because of the duration of treatment (should be 14 days), the drug interaction with warfarin, as well as the patient's renal function (Answer A is incorrect). Ciprofloxacin 400 mg intravenously twice daily and then 500 mg orally twice daily for 7 days is an appropriate choice and duration for this complicated pyelonephritis (it may also interact with warfarin but to a lesser extent than trimethoprim/sulfamethoxazole). It would be expected to have activity against the common organisms causing complicated pyelonephritis (Answer B is correct). Gentamicin for 3 days is too short a treatment duration (Answer C is incorrect). Tigecycline, followed by doxycycline, is not recommended for complicated pyelonephritis (although tigecycline is found unchanged in the urine) (Answer D is incorrect).

5. Answer: C

Nafcillin has excellent activity against gram-positive organisms, but it would miss the gram-negative organisms and anaerobes often involved in moderate to severe diabetic foot infections (Answer A is incorrect). Tobramycin and levofloxacin would be good against aerobic organisms, but levofloxacin has no activity against anaerobes. Tobramycin may also not be a good choice for a patient with diabetes with long-term complications (because of the increased risk of nephrotoxicity) (Answer B is incorrect). β-Lactamase inhibitor combinations are good agents because they have activity against the organisms that are often involved. At this time, a regimen active

against *P. aeruginosa* is probably necessary because of a macerated ulcer occurring in a temperate climate and water exposure. Treatment duration may need to be extended if the bone is involved (Answer C is correct). Aggressive antibiotic treatment often prevents the need for an amputation (Answer D is incorrect).

6. Answer: A
Because sensitivities of the gram-positive organism are still unknown, vancomycin is the best choice. In addition, the therapy duration for osteomyelitis is 4–6 weeks (Answer A is correct). Therefore, the 2-week duration with nafcillin is too short (Answer B is incorrect). Although levofloxacin is advantageous because it can be given orally, it will probably not achieve adequate bone concentrations to eradicate *S. aureus* (the most likely organism) (Answer C is incorrect). Ampicillin/sulbactam is effective against *S. aureus* (except for MRSA); its broad spectrum of activity is not necessary in this situation, and the duration is too short (Answer D is incorrect).

7. Answer: D
From his presentation and laboratory values, this patient has bacterial meningitis. Penicillin is effective against *N. meningitidis* and *S. pneumoniae;* however, some strains are resistant, and until culture results are received, it is unwise to use this agent alone (Answer A is incorrect). Ceftriaxone alone is effective for meningococcal and pneumococcal meningitis; however, vancomycin should be started empirically with ceftriaxone in case the patient has a highly penicillin-resistant *S. pneumoniae* (Answers B and C are incorrect). Ceftriaxone is the appropriate empiric antibiotic therapy in this situation and vancomycin is generally used empirically because of its activity against highly penicillin-resistant *S. pneumoniae* (Answer D is correct). The vancomycin can be discontinued when highly penicillin-resistant pneumococcal meningitis is ruled out.

8. Answer: A
Only people in close contact to a patient with meningococcal meningitis need prophylaxis (primarily those who live closely with the patient and those who are exposed to oral secretions) (Answer B and D are incorrect). The correct regimen is rifampin 600 mg every 12 hours for four doses (Answer A is correct). Although the vaccine is a good idea for those at future risk of acquiring this infection (e.g., college students living in dormitories), its use during an outbreak is very limited (Answer C is incorrect).

9. Answer: D
A treatment duration of 7-10 days is too short for *S. aureus* endocarditis in the mitral position (Answer A is incorrect). Only streptococcal endocarditis can be treated for 2 weeks. Although nafcillin intravenously plus rifampin plus gentamicin therapy for 6 weeks or longer is an appropriate duration for MSSA, the rifampin and gentamicin need not be added in patients with native valve endocarditis (Answer B is incorrect). Nafcillin intravenously plus gentamicin intravenously for 2 weeks is too short for *S. aureus* endocarditis (Answer C is incorrect). Nafcillin intravenously for 6 weeks is the recommended treatment for MSSA endocarditis (Answer D is correct).

10. Answer: B
This patient is at increased risk of endocarditis because of his history of the disease (Answer D is incorrect). Tooth extractions warrant prophylaxis for those at risk (Answer A is incorrect) Amoxicillin 2 g, 1 hour before the tooth extraction, is the current recommended dose (Answer B is correct). The 2-g dose is adequate for protection, and a follow-up dose is not needed. Amoxicillin 3 g 1 hour before the extraction and 1.5 g 6 hours for four doses after the extraction is the older recommended dose. A follow-up dose is not needed (Answer C is incorrect).

11. Answer: B
This patient is having a severe episode of *C. difficile* diarrhea, as demonstrated by his low albumin, high WBC, and elevated SCr. Therefore, metronidazole is not the optimal choice (and the duration is too short) (Answer A is incorrect). Rifaximin is not a first-line agent (Answer D is incorrect). Fidaxomicin could be used first line in patients who are at high risk of recurrence, but the duration of 14 days is too long (Answer C is incorrect). The best therapy for this patient is vancomycin for 10 days (Answer B is correct).

12. Answer: A
Redosing antibiotics for surgical prophylaxis is very important, especially for antibiotics with short half-lives, for extended surgical procedures, or for when there is extensive blood loss (Answer A is correct).

Antibiotics given beyond the surgical procedure are generally unnecessary and only increase the potential for adverse drug reactions and resistant bacteria (Answer B is incorrect). Although preoperative antibiotics given up to 4 hours before the incision may improve the logistics of administering surgical prophylaxis, study results show that antibiotics must be given as close to the time of the incision as possible (definitely within 2 hours) (Answer C is incorrect). Vancomycin should not be used routinely for surgical prophylaxis. The Centers for Disease Control and Prevention does not recommend the use of vancomycin for "routine surgical prophylaxis other than in a patient with life-threatening allergy to β-lactam antibiotics."(Answer D is incorrect).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: A

The patient has CAP that does not require hospitalization (PSI score is 56, class II, which is low risk). Because he has not received any antibiotics in the past 3 months and has no comorbidities, he is at low risk of DRSP. Therefore, the drug of choice is either a macrolide or doxycycline (Answer A is correct). Cefuroxime is not recommended for the treatment of CAP (Answer B is incorrect). Fluoroquinolones are recommended only if the patient has had recent antibiotics or has comorbidities (Answer C is incorrect). Trimethoprim/sulfamethoxazole is not used for CAP (Answer D is incorrect).

2. Answer: D

The symptoms of this patient (high temperature, malaise, dry cough, nasal congestion, and severe headaches) are most consistent with influenza; therefore, an antibacterial agent would not affect recovery (Answers A and B are incorrect). Oseltamivir should be initiated within 48 hours of symptom onset, so because this patient is more than 3 days out from symptom onset, oseltamivir will not affect recovery (Answer C is incorrect). Because of the viral etiology and time since symptom onset, symptomatic treatment is all that is indicated (Answer D is correct).

3. Answer: B

A case-control study would be the most appropriate study design because it is the most ethical, cost-effective, timely method (Answer B is correct). A stronger study design—for instance, a prospective cohort study or a randomized controlled trial—has many disadvantages if used to answer this question. In a prospective cohort study, too many patients would need to be observed because of the low incidence of confirmed pneumococcal pneumonia. This study would be too costly and take too long to complete (Answer C is incorrect). Randomized controlled trials also have many disadvantages in this situation. First, patients would need to be vaccinated and then observed for at least 10 years. Second, too many patients would need to be observed because of the low incidence of confirmed pneumococcal pneumonia. Third, it would be unethical to randomly assign half of the patients to no vaccination. This study would therefore be too costly, unethical, and time-consuming (Answer D is incorrect). A case series would evaluate only a few patients given a diagnosis of pneumococcal pneumonia 10 years or more after vaccination. It would not provide comparative data, nor would it provide a strong study design (Answer A is incorrect).

4. Answer: C

Although necrotizing fasciitis can be caused by *Streptococcus* only, it is often a mixed infection that includes gram-positive, gram-negative, and anaerobic bacteria. Therefore, in addition to urgent surgical debridement, it must be treated empirically with broad-spectrum antibiotics. It is recommended that one of those antibiotics have activity against *P. aeruginosa*. Clindamycin or linezolid therapy is also recommended initially to decrease the production of toxin by *Streptococcus*. Because vancomycin alone has no activity against gram-negative organisms and does not decrease toxin production, it is not the best empiric agent (Answer A is incorrect). Moreover, piperacillin/tazobactam alone has no activity against MRSA and does not decrease toxin production (Answer B is incorrect). Although there are some data that azithromycin may also decrease toxin production and that linezolid has MRSA activity, ceftriaxone has no activity against *P. aeruginosa* (Answer D is incorrect). The best empiric option is vancomycin plus meropenem plus clindamycin (Answer C is correct).

5. Answer: C

Although nitrofurantoin is a recommended first-line agent, the therapy duration is too short for its use (Answer A is incorrect). Because this patient has no contraindications to the use of trimethoprim/sulfamethoxazole or nitrofurantoin, and trimethoprim/sulfamethoxazole resistance rates are not mentioned as being high, fluoroquinolones would not be considered appropriate as first-line therapy in this particular case (Answer B is incorrect). In addition, 7 days of therapy is not necessary. The best choice for this patient is trimethoprim/sulfamethoxazole double strength twice daily orally for 3 days. The patient should be counseled about the potential interaction between antibiotics and oral contraceptives (Answer C is correct). β-Lactams are not as effective as trimethoprim/sulfamethoxazole, and data are limited on their use for 3 days (Answer D is incorrect).

6. Answer: A

For the asymptomatic patient who is bedridden and chronically catheterized, with cloudy urine and bacteria revealed by urinalysis, no therapy is indicated (Answer A is correct). All patients with chronic urinary catheters will be bacteriuric. Because this patient is asymptomatic, the catheter does not need to be replaced (Answer B is incorrect). If she were symptomatic, catheter replacement might be indicated. Antibiotics are not indicated; however, a 7-day course would be appropriate if treatment were instituted (Answer C and D are incorrect). A long course of treatment only increases the risk of acquiring resistant organisms.

7. Answer: A

Because cellulitis (which the patient appears to have) is usually caused by *Streptococcus* or *Staphylococcus*, cefazolin is the drug of choice (vancomycin could be initiated empirically if MRSA were a concern in this patient) (Answer A is correct). Although penicillin is the treatment of choice for erysipelas, the patient probably has acute cellulitis (there is no raised border at the edge of the infection, which indicates erysipelas) (Answer B is incorrect). Although piperacillin/tazobactam has activity against both *Streptococcus* and *Staphylococcus,* this treatment is too broad spectrum for an acute cellulitis (Answer C is incorrect). Because the patient is febrile with extensive cellulitis, oral antibiotics are not appropriate at this time (Answer D is incorrect).

8. Answer: C

Even if a patient is believed to have aseptic meningitis after analysis of the CSF, antibiotics must be given until CSF cultures are negative (Answer A is incorrect). In empiric therapy for bacterial meningitis in adults (i.e., when the CSF Gram stain is negative), ceftriaxone should be used in combination with vancomycin (Answer B is incorrect). The vancomycin is necessary for activity against resistant *S. pneumoniae (*Answer C is correct). Although the symptoms and CSF results are similar to what is expected for herpes simplex encephalitis, the use of acyclovir alone in this patient is inappropriate. Antibacterials must be used as well. Viral meningitis is generally caused by coxsackievirus, echovirus, and enterovirus, which are not treated with acyclovir (Answer D is incorrect).

9. Answer: C

Enterococcal endocarditis should be treated for 4–6 weeks. The 2-week treatment regimen is indicated only for streptococcal endocarditis *(*Answer A is incorrect). There is also no indication that the patient is penicillin allergic; thus, vancomycin should not be used as first-line treatment (Answer B is incorrect). Ampicillin plus ceftriaxone for 6 weeks is a regimen of choice for penicillin-susceptible enterococcal endocarditis (Answer C is correct). Cefazolin has no activity against *Enterococcus;* therefore, the regimen with cefazolin is inappropriate (Answer D is incorrect).

10. Answer: C

A perforated appendix requires antibiotics after surgery for an intra-abdominal infection (Answer D is incorrect). The combination of vancomycin and metronidazole does not have adequate activity against aerobic, gram-negative organisms (e.g., *E. coli*) (Answer A is incorrect). The combination of cefazolin and ciprofloxacin does not have adequate activity against anaerobic organisms (e.g., *B. fragilis* group) (Answer B is incorrect). Ceftriaxone plus metronidazole is a good choice for intra-abdominal infections, although it has limited activity against *Enterococcus* (Answer C is correct).

11. Answer: D

β-Lactam antibiotics are not recommended first-line agents for patients with acute bacterial prostatitis. Therefore, amoxicillin/clavulanate and cefprozil are not the best options in this patient (Answers A and C are incorrect). Although trimethoprim/sulfamethoxazole is an appropriate antibiotic, 7 days of treatment is too short for prostatitis. Treatment duration should be 4 weeks (Answer B is incorrect). Fluoroquinolones are an appropriate antibiotic class for prostatitis, and the 28-day duration is also appropriate (Answer D is correct).

12. Answer: B

Because the organism causing the infection is known to be MSSA, using vancomycin or daptomycin is unnecessary. They both can potentially cause serious toxicities, and daptomycin is expensive (Answers A and D are incorrect). Both nafcillin and cefazolin are appropriate choices for MSSA osteomyelitis; however, because this infection involves a prosthetic joint rifampin must be combined with the primary antibiotic, and

this combination must continue for 2–6 weeks (Answer C is incorrect). This must be followed with 3 months of appropriate oral antibiotics. (Answer B is correct).

13. Answer: A

For any orthopedic surgical procedures in which prosthetic materials will be implanted, surgical prophylaxis is necessary. The preferred agent is cefazolin, although vancomycin may be used in patients with allergies. The recommended dosage of cefazolin is at least 2 g (3 g for those weighing more than 120 kg) (Answers C and D are incorrect). Antibiotics must be present in the tissues at the time of incision, and it is best to administer the agent within 1 hour of the incision (Answer A is correct). Because orthopedic procedures tend to be shorter procedures, redosing is probably unnecessary. Administering antibiotics beyond surgical closure is unnecessary (Answer B is incorrect).

Infectious Diseases II

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Learning Objectives

1. Formulate an appropriate regimen to prevent or treat HIV infections, including initiating and monitoring therapy.
2. Discuss appropriate treatment of the various acquired immunodeficiency syndrome opportunistic infections, including primary and secondary prophylaxis.
3. Describe appropriate treatment and preventive therapy for tuberculosis, including infections with drug-resistant organisms.
4. Design appropriate therapeutic regimens for treating systemic and superficial fungal infections.

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

1. K.E. is a 29-year-old asymptomatic patient who is HIV positive. She recently found out she is pregnant and is estimated to be early in her first trimester. Her most recent CD4 count was 170 cells/mm^3, and her viral load was 100,000 copies/mL by reverse transcriptase polymerase chain reaction. Which is the best therapy for K.E. to prevent HIV transmission to her child?
   A. No drug therapy is needed; the risks to the fetus outweigh any benefits.
   B. Administer zidovudine 300 mg twice daily orally throughout the pregnancy, followed by zidovudine during labor and subsequently to the infant for 6 weeks.
   C. No drug therapy is needed now, but administer a single dose of nevirapine at the onset of labor.
   D. Administer a potent combination antiretroviral therapy (ART) regimen.

2. R.E. is a 33-year-old man who recently tested HIV positive. He is initiated on tenofovir alafenamide, emtricitabine, and dolutegravir. Which is the best counseling for R.E.?
   A. Watch for trouble sleeping because dolutegravir can cause insomnia.
   B. If you think you are having a drug-related adverse effect, cut the dose of all of your drugs in half.
   C. Talk to your pharmacist about drug interactions because both dolutegravir and tenofovir inhibit cytochrome P450 (CYP) 3A4.
   D. Tenofovir and emtricitabine cause additive peripheral neuropathy, so let your pharmacist know if you have tingling in your extremities.

3. P.P., a 43-year-old man who is HIV positive, presents to the clinic with a headache that has gradually worsened during the past 2 weeks. He does not feel very sick and has not experienced any focal seizures. His most recent CD4 count was 35 cells/mm^3. After a lumbar puncture is performed, he is given a diagnosis of cryptococcal meningitis and successfully treated. Which is the best follow-up therapy for P.P.?
   A. No maintenance treatment is necessary.
   B. Administer fluconazole 200 mg daily orally.
   C. Administer amphotericin B 1 mg/kg weekly intravenously.
   D. He is protected as long as he is also receiving *Pneumocystis jiroveci* pneumonia (PJP) prophylaxis.

4. A study compares the incidence of active tuberculosis (TB) infection in patients receiving isoniazid versus rifampin for latent TB infection. After completing therapy (6 months for isoniazid and 4 months for rifampin), 0.3% in the isoniazid group and 0.8% in the rifampin group progress to active disease. Which best represents how many patients would need to be treated with isoniazid over rifampin to prevent one progression to active disease?
   A. 5.
   B. 50.
   C. 200.
   D. 2000.

5. G.T. is a 34-year-old woman positive for HIV who is brought to the emergency department by her boyfriend after experiencing headaches, a change in mental status, and loss of feeling on her right side. A computed tomographic scan shows two large ring-enhancing lesions in her brain indicating toxoplasmic encephalitis. Her most recent CD4 count was 85 cells/mm^3, but that was 4 months ago. She currently takes no antiretroviral agents but

does take dapsone for PJP prophylaxis. Which is the best therapy for G.T.?

A. Atovaquone for 4–6 weeks.
B. High-dose trimethoprim/sulfamethoxazole plus clindamycin for 6 weeks.
C. Pyrimethamine plus sulfadiazine for 6 weeks.
D. Pyrimethamine plus clindamycin and leucovorin for 6 weeks.

6. H.Y., a 49-year-old man with acute myeloid leukemia, is given a diagnosis of tuberculosis (TB) and initiated on empiric therapy with rifampin, isoniazid, ethambutol, and pyrazinamide. Three months into his TB therapy, he is hospitalized and given a diagnosis of aspergillosis; treatment is needed in addition to his TB treatment. Which is the best antifungal to use in H.Y.?

A. Fluconazole.
B. Voriconazole.
C. Isavuconazonium.
D. Amphotericin lipid formulation.

7. P.I. is a 35-year-old woman who presents to the clinic with a 2-week history of night sweats, fatigue, weight loss, and a persistent cough. A tuberculin skin test (TST) is placed, and a sputum sample is taken; then, P.I. is sent home with a prescription for levofloxacin 750 mg daily orally. Two days later, her TST is measured at 20-mm induration, and her sputum sample is positive for acid-fast bacilli. P.I., who has no pertinent medical history, has never been outside the United States. She lives in an area with an extremely low incidence of multidrug-resistant TB. Which regimen is the best therapy for P.I.?

A. Isoniazid for 6 months.
B. Isoniazid, rifampin, pyrazinamide, and ethambutol for 2 months, followed by isoniazid and rifampin for 4 more months.
C. Isoniazid and rifampin for 6 months.
D. Levofloxacin, isoniazid, and rifampin for both TB and other bacterial causes of pneumonia.

8. A prospective, double-blind study compared the effects of two therapies—a potent combination ART with a ritonavir-boosted protease inhibitor (PI) and a potent combination ART with dolutegravir—in 350 patients with HIV. Which is the best statistical test to use to compare end points such as the mean change in viral load or mean change in CD4 counts?

A. Analysis of variance.
B. Chi-square test.
C. Student t-test.
D. Wilcoxon rank sum test.

9. J.Z. is a 42-year-old HIV-positive man with a diagnosis of cytomegalovirus (CMV) retinitis 9 months ago. Since then, he has been treated with valganciclovir. When he received a diagnosis of CMV retinitis, his CD4 count was 17 cells/mm^3, and he was initiated on combination ART. Three months ago, his CD4 count was 175 cells/mm^3. Today, his CD4 count is 312 cells/mm^3. Which is the best recommendation for valganciclovir therapy in J.Z.?

A. Discontinue valganciclovir because his CD4 count has been above 100 cells/mm^3 for 3 months.
B. Continue valganciclovir until the CD4 count has been above 100 cells/mm^3 for 1 year.
C. Finish 1 year of therapy with valganciclovir and then discontinue the medication if his CD4 count is still above 100 cells/mm^3.
D. Continue valganciclovir indefinitely.

10. K.T. is a 55-year-old woman who is hospitalized with a presumed *Candida* infection. She currently receives simvastatin, diazepam, lisinopril, dofetilide, and metoprolol. Which antifungal would be best to use empirically with the other medications K.T. is receiving?

A. Liposomal amphotericin B.
B. Fluconazole.
C. Micafungin.
D. Olorofim.

11. T.E. is a 51-year-old man who has been HIV positive for 23 years. He is hospitalized for cellulitis and reports that he has not taken his ART for at least a year. His current CD4 count is 112 cells/mm^3. He is allergic to penicillins and sulfonamide antibiotics. Which regimen is the best PJP prophylaxis for T.E.?

A. Trimethoprim/sulfamethoxazole one double-strength tablet by mouth daily.

B. Dapsone 100 mg by mouth weekly.

C. Atovaquone 1500 mg by mouth daily.

D. Pentamidine 300 mg by nebulization once monthly.

12. O.D. is a 38-year-old HIV positive man originally from Puerto Rico who moved to the continental United States four years ago. He is hospitalized for fever, weight loss, chills, myalgia, and lymphadenopathy. He is initially treated for PJP but his symptoms worsen. A bronchoscopy is performed and the cultures are positive for *Histoplasma capsulatum*. What is the best treatment for O.D.?

A. Amphotericin B lipid formulation for 1-2 weeks followed by itraconazole 200 mg three times daily for 3 days followed by 200 mg twice daily for 12 weeks total.

B. Micafungin 100 mg IV daily for 1-2 weeks followed by fluconazole 400 mg daily for 12 weeks total.

C. Voriconazole 200 mg twice daily for 6 weeks total.

D. Isavuconazole 200 mg every 8 hours for 2 days followed by 200 mg daily for 6 weeks total.

13. R.V. is a 35-year-old man who presents to the emergency department with a persistent cough, night sweats, and an unintentional 15 kg recent weight loss. He has experienced homelessness for over 3 years and has been living at multiple shelters in the city. An interferon-gamma release assay test is positive and his sputum is acid-fast bacillus positive. He is not HIV-infected. Which one of the following would be the best empiric therapy for R.V.?

A. Rifampin, isoniazid, pyrazinamide, and ethambutol 3 times weekly for 2 months followed by rifampin and isoniazid 2 times weekly for 4 months.

B. Rifampin, isoniazid, pyrazinamide, and ethambutol daily for 2 months followed by rifampin and isoniazid 5 times weekly for 4 months.

C. Rifampin, isoniazid, pyrazinamide, and ethambutol daily for 2 months followed by rifampin, isoniazid, and ethambutol 3 times weekly for 4 months.

D. Rifampin, isoniazid, pyrazinamide, and ethambutol 5 times weekly for 2 months followed by rifampin, isoniazid, and pyrazinamide 2 times weekly for 4 months.

BPS Pharmacotherapy Specialty Examination Content Outline

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline, tested during the Spring 2024 window:

1. Patient-Centered Pharmacotherapy
   a. 1.1. Develop patient-centered, evidence-based pharmacotherapy plans. Subtasks: 1.1.1 – 1.1.4, 1.1.6, 1.1.8, 1.1.10, 1.1.11, 1.1.14.
   b. 1.2. Monitor the patient to ensure safe and effective pharmacotherapy. Subtasks: 1.2.1 – 1.2.3.
   c. 1.3. Modify pharmacotherapy plans through ongoing patient assessment. Subtasks: 1.3.1 – 1.3.4.
3. Healthcare Systems and Population Health
   a. 3.3. Incorporate public health initiatives to improve population health. Subtask: 3.3.2.

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline, tested starting Fall 2024:

1. Patient Care Specialty Areas
   a. 1A. Primary Pharmacotherapy Specialty Areas. Subtask: 1A1.
2. Therapeutics and Patient Management
   b. 2A. Treatment Planning. Subtasks: 2A1 – 2A5.
   c. 2B. Therapeutic Implementation. Subtasks: 2B1, 2B2.
   d. 2C. Treatment Outcomes and Monitoring. Subtasks: 2C1 – 2C5.
3. Professional Practice
   a. 3A. Quality of Care. Subtasks: 3A1, 3A2, 3A4.
   b. 3C. Practice Management. Subtasks: 3C1, 3C2.

I. HUMAN IMMUNODEFICIENCY VIRUS (HIV)

A. Transmission of HIV
   1. Sexual transmission
      a. Vaginal, anal, or oral sex
      b. Increases with increased number of unprotected sexual encounters
   2. Parenteral exposure to blood or blood products
      a. Persons who inject drugs; Increased with used needle sharing
   3. Perinatal transmission
      a. Antepartum: Through maternal circulation
      b. During delivery
      c. Postpartum: Breastfeeding
      d. Zidovudine therapy decreases the risk of transmission from 23% to 3%–4% (less than 2% with combination therapy). The goal of the Centers for Disease Control and Prevention is to decrease transmissions to less than 1% through suppressive combination antiretroviral therapy (ART) administered throughout pregnancy.

B. Diagnosis

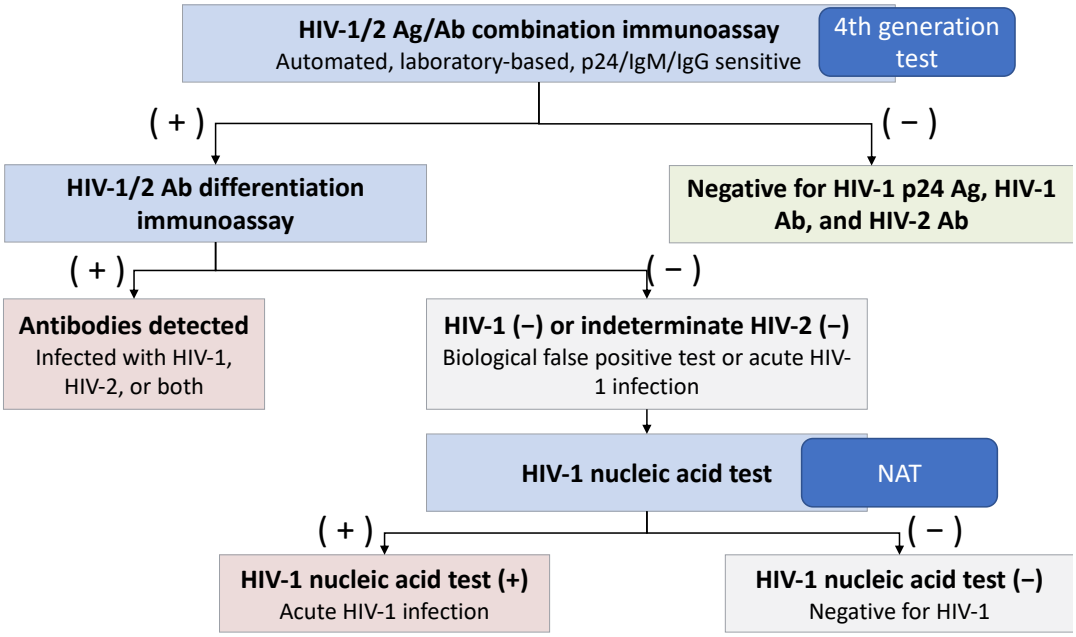

HIV-1/2 Ag/Ab combination immunoassay
Automated, laboratory-based, p24/IgM/IgG sensitive
4th generation test
(+)
(−)
HIV-1/2 Ab differentiation immunoassay
Negative for HIV-1 p24 Ag, HIV-1 Ab, and HIV-2 Ab
(+)
(−)
Antibodies detected
Infected with HIV-1, HIV-2, or both
HIV-1 (−) or indeterminate HIV-2 (−)
Biological false positive test or acute HIV-1 infection
HIV-1 nucleic acid test
NAT
(+)
(−)
HIV-1 nucleic acid test (+)
Acute HIV-1 infection
HIV-1 nucleic acid test (−)
Negative for HIV-1

Figure 1. Outpatient HIV testing.

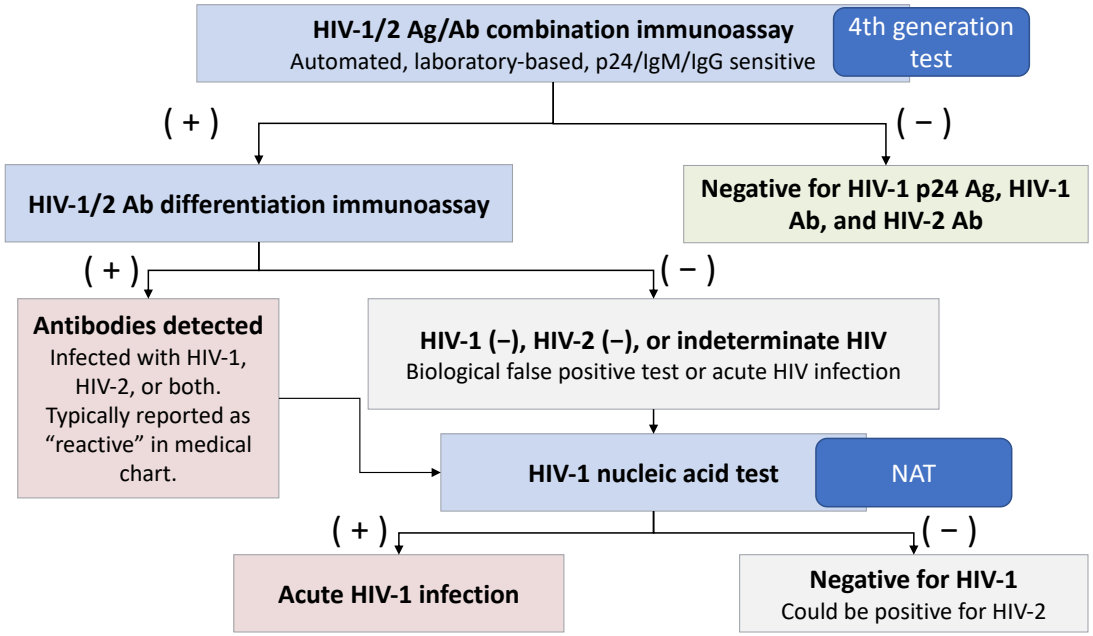

HIV-1/2 Ag/Ab combination immunoassay
Automated, laboratory-based, p24/IgM/IgG sensitive
4th generation test
(+)
(–)
HIV-1/2 Ab differentiation immunoassay
Negative for HIV-1 p24 Ag, HIV-1 Ab, and HIV-2 Ab
(+)
(–)
Antibodies detected
Infected with HIV-1, HIV-2, or both. Typically reported as "reactive" in medical chart.
HIV-1 (–), HIV-2 (–), or indeterminate HIV
Biological false positive test or acute HIV infection
HIV-1 nucleic acid test
NAT
(+)
(–)
Acute HIV-1 infection
Negative for HIV-1
Could be positive for HIV-2

Figure 2. Inpatient HIV testing.

1. Step 1
   a. Fourth-generation HIV test
   b. Window period: 18–45 days
   c. Negative tests require no further testing; positive tests proceed to step 2.
   d. Sensitivity and specificity: Greater than 99%
2. Step 2
   a. HIV test that differentiates HIV-1 from HIV-2
   b. If positive, diagnosis is made
   c. If negative or indeterminate, proceed to step 3
   d. Sensitivity and specificity: Greater than 99%
3. Step 3
   a. HIV-1 nucleic acid amplification test (screening for HIV-1 RNA)
   b. If positive, diagnosis is made
   c. If negative, negative for HIV-1
4. Rapid HIV testing
   a. Oral swab or fingerstick
   b. Results within 20 minutes; window period: 26–90 days
   c. Negative test result: HIV negative
   d. Positive test result: Repeat with a different manufacturer's test. If positive, HIV positive (refer for appropriate care)
   e. If first test is positive and second test is negative, repeat with a different manufacturer's test. If repeat test is positive, HIV positive; if negative, HIV negative
5. Test for HIV RNA (viral load)
   a. Detects HIV RNA in serum (tests for the virus, not for antibodies)
   b. Values expressed as copies of HIV RNA per milliliter or the log of copies of HIV RNA per milliliter
   c. Viral suppression, defined as HIV RNA below the level of detection of the assay (HIV RNA less than 20 copies/mL to 75 copies/mL), is the goal of treatment.
   d. While on treatment, changes greater than 3-fold (about 0.5 log) are statistically significant.

6. Use of HIV RNA testing (viral load)
    a. Most important use of the viral load is to monitor the effectiveness of therapy after initiation of ART.
    b. Newly diagnosed HIV infection (for baseline value to follow)
    c. Every 3–6 months without therapy
    d. From 2 to 4 (no more than 8) weeks after starting or changing therapy (should detect a significant decrease)
    e. Every 3–4 months while on therapy (to check for increase—which would indicate therapy failure). May consider extension to every 6 months in patients on therapy and suppressed greater than 1 year with immune stability
    f. Whenever there is a clinical event or decrease in CD4 count
7. CD4 T-cell count
    a. Measure of immune function, used to determine the urgency of ART, opportunistic infection prophylaxis, disease progression, and survival
    b. Changes greater than 30% in CD4 counts are considered clinically significant.
    c. CD4 counts decrease, on average, 50–80 cells/mm^3 per year in untreated HIV-infected patients.
    d. With potent combination ART, CD4 counts increase, on average, 50–100 cells/mm^3 per year.
    e. Monitor at diagnosis (baseline), after ART is started to guide discontinuation of opportunistic infection prophylaxis, every 12 months for those consistently on therapy and with CD4 counts between 300 and 500 cells/mm^3 for at least 2 years, and optional if CD4 is greater than 500 cells/mm^3 in those virologically suppressed for at least 2 years. More frequent monitoring (every 3–6 months) may be needed based on clinical symptoms and viral load testing.
8. Who should be screened for HIV?
    a. All patients 13–64 years of age at least once
    b. Adults and adolescents at high risk of HIV infection should be checked annually, including the following: persons who inject drugs and share needles/syringes, those who have sex with more than one partner, men who have sex with men, men or women who have sex for money or drugs, anyone who has had sex with someone who has HIV, people being treated for sexually transmitted infections, people diagnosed or treated for hepatitis or tuberculosis, and persons who have had sex with anyone with one of these risk factors, or whose sexual history is unknown.
    c. Pregnant women – As early as possible and repeat testing in the third trimester
9. AIDS-defining conditions (Table 1)

Table 1. AIDS-Defining Conditions

Bacterial infections, multiple or recurrent (< 6 yr)	Lymphoma: Burkitt (or equivalent term)
Candidiasis: bronchi, trachea, or lungs	Lymphoma: immunoblastic (or equivalent term)
Candidiasis: esophageal	Lymphoma: primary, of brain
Cervical cancer: invasive (≥ 6 yr)	*Mycobacterium avium* complex or *M. kansasii*: disseminated or extrapulmonary
Coccidioidomycosis: disseminated or extrapulmonary	*M. tuberculosis:* any site (pulmonary, disseminated, or extrapulmonary)
Cryptococcosis: extrapulmonary	*Mycobacterium*: other species or unidentified species; disseminated or extrapulmonary
Cryptosporidiosis: chronic intestinal (> 1 mo in duration)	*Pneumocystis jiroveci* pneumonia
Cytomegalovirus disease (other than liver, spleen, or nodes)	Pneumonia: recurrent
Cytomegalovirus retinitis (with loss of vision)	Progressive multifocal leukoencephalopathy
Encephalopathy: HIV related	*Salmonella* septicemia (recurrent)
Herpes simplex: chronic ulcer(s) (> 1 mo in duration); bronchitis, pneumonitis, or esophagitis	Toxoplasmosis of brain
Histoplasmosis: disseminated or extrapulmonary	Wasting syndrome caused by HIV
Isosporiasis: chronic intestinal (> 1 mo in duration)	
Kaposi sarcoma	

C. Prevention of HIV
   1. Universal precautions (Table 2)
      a. Purpose is prevention of parenteral, mucous membrane, and non-intact skin exposures to blood-borne pathogens.

Table 2. Universal Precautions

Universal Precautions Apply to:	Universal Precautions Do Not Apply to:
Blood	Feces
Bodily fluids containing visible blood	Nasal secretions
Semen and vaginal secretions	Sputum
Tissue	Sweat
Cerebrospinal fluid	Tears
Synovial fluid	Urine
Pleural fluid	Vomitus
Peritoneal fluid	Breast milk
Pericardial fluid	Saliva (precautions recommended for dentistry)
Amniotic fluid	

      b. General guidelines
         i. Take care when using and disposing of needles, scalpels, and other sharp instruments.
         ii. Use protective barriers (e.g., gloves, masks, and protective eyewear).
         iii. Wash hands and skin immediately if they are contaminated with body fluids to which universal precautions apply.
   2. Nonpharmacologic prevention
      a. Latex or polyurethane condoms
      b. Circumcision (males)
   3. Pharmacologic prevention
      a. Use in sexually active individuals who recently tested negative for HIV
         i. PrEP options for any individual that requests it and who has recently tested negative for HIV
            (a) Tenofovir disoproxil fumarate 300 mg plus emtricitabine 200 mg orally daily
            (b) Tenofovir alafenamide 25 mg plus emtricitabine 200 mg orally daily (only in individuals born biologically male)
            (c) Cabotegravir 600 mg in months 1 and 2, then every 8 weeks thereafter (optional oral lead-in)
         ii. On-demand PrEP
            (a) Tenofovir disoproxil fumarate 300 mg plus emtricitabine 200 mg, administered as 2-1-1 dosing: 2 doses 2–24 hours before sex (closer to 24 hours preferred), 1 dose 24 hours after the first dose, and 1 dose 48 hours after the first dose.
            (b) Option for men who have sex with men, who do not want daily PrEP dosing, have sex infrequently, and can anticipate when they will have sex
            (c) No FDA approval at this time.
         iii. Retest for HIV every 3 months after PrEP initiation (following HIV testing algorithm) or every 2 months when cabotegravir is used as prophylaxis (using HIV-1 RNA assay)
         iv. The following laboratory values should be checked prior to PrEP initiation and at least every 6–12 months:
            (a) Renal function with tenofovir
            (b) Bacterial STI screening
            (c) Lipid profile

b. Treatment as prevention (TasP)
    i. Maintaining HIV RNA less than 200 copies/mL with ART prevents HIV transmission to sexual partners.
    ii. Other forms of prevention should be used during the first 6 months of treatment and until the HIV RNA is less than 200 copies/mL.
    iii. Adherence is crucial for TasP.
c. Prevention of maternal-fetal transmission
    i. Pregnant women with HIV not receiving ART
        (a) All HIV-infected pregnant women should receive combination ART; initiate therapy as soon as possible, even in the first trimester.
        (b) Preferred regimens for HIV-infected pregnant women include a dual nucleoside reverse transcriptase inhibitor (NRTI) combination (abacavir/lamivudine, or tenofovir/emtricitabine or tenofovir/lamivudine) plus either a ritonavir-boosted protease inhibitor (PI) (darunavir/ritonavir) or an integrase strand transfer inhibitor (INSTI) (dolutegravir).
        (c) All women should have HIV antiretroviral resistance testing completed.
        (d) Continue combination regimen through intrapartum period.
    ii. Pregnant women with HIV receiving potent combination ART
        (a) Continue current combination regimens if already receiving therapy.
            (1) Specific regimen changes may be necessary including, but not limited to, replacing elvitegravir/cobicistat or more frequent dosing of darunavir.
        (b) Continue combination regimen through intrapartum period.
    iii. Pregnant women with HIV in labor (with or without therapy during pregnancy)
        (a) Intravenous zidovudine should be administered to HIV-infected women with an HIV RNA greater than 1000 copies/mL (or unknown HIV RNA) near delivery. Consideration can also be given to treating women with an HIV RNA of 50–1000 copies/mL. Intravenous zidovudine is not necessary for HIV-infected women with an HIV RNA of 50 copies/mL or less during late pregnancy who are near delivery and in whom there are no concerns about adherence to their ART regimen.
        (b) Continue combination ART during labor as able.
    iv. Infants born to mothers who are HIV positive
        (a) Low risk of perinatal HIV transmission: Zidovudine 4 mg/kg/dose every 12 hours for 4 weeks, initiated within 6 hours of delivery
        (b) Higher risk of perinatal transmission or presumed HIV exposure: Presumptive HIV therapy with zidovudine, lamivudine, and nevirapine OR zidovudine, lamivudine, and raltegravir. Presumptive therapy should continue for 6 weeks.
d. Post-exposure prophylaxis (PEP)
    i. Use universal precautions.
    ii. Post-exposure prophylaxis can reduce HIV infection by about 80%.
    iii. Nonoccupational exposures (nPEP)
        (a) Treat if exposure of vagina, rectum, eye, mouth, mucous membrane, or non-intact skin with blood, semen, vaginal secretions, or breast milk of a person with a known HIV infection
        (b) Begin prophylaxis within 72 hours. Treatment should be administered for 4 weeks.
        (c) Preferred regimen: Raltegravir twice daily or dolutegravir daily plus tenofovir disoproxil fumarate/emtricitabine daily
        (d) Alternative regimen: Darunavir/ritonavir daily plus tenofovir disoproxil fumarate/emtricitabine daily

iv. Occupational exposures
(a) Needlesticks or cuts (1 in 300 risk) and mucous membrane exposure (1 in 1000 risk)
(b) Begin treatment within hours; if HIV status of source patient is unknown, start treatment while status is being evaluated. Treatment should be administered for 4 weeks.
(c) Preferred regimen: Raltegravir twice daily plus tenofovir disoproxil fumarate/emtricitabine
(d) Alternative regimens:
(1) One of the following agents: Raltegravir, darunavir/ritonavir, etravirine, rilpivirine, atazanavir/ritonavir, or lopinavir/ritonavir plus one of the following combinations: tenofovir disoproxil fumarate/emtricitabine, tenofovir disoproxil fumarate/lamivudine, zidovudine/lamivudine, or zidovudine/emtricitabine
(2) Elvitegravir, cobicistat, tenofovir disoproxil fumarate, emtricitabine (Stribild)
(3) Elvitegravir, cobicistat, tenofovir alafenamide

D. Treatment of HIV
1. Reverse transcriptase inhibitors (RTIs) (nucleoside/nucleotide [NRTIs] and nonnucleoside [NNRTIs])
a. Reverse transcriptase: Enzyme needed to copy viral RNA to DNA
b. See Tables 3 and 4 for RTI characteristics.
2. Protease inhibitors (PIs)
a. Protease: Enzyme needed to cleave polyproteins into mature viral protein components
b. See Table 5 for PI characteristics.
3. Integrase inhibitors (INSTIs)
a. Integrase: Enzyme needed for integration of viral DNA into the host cellular genome
b. See Table 6 for INSTI characteristics.
4. Entry and post-attachment inhibitors
a. Block binding and/or entry of the virus into human cells
b. See Table 7 for entry and post-attachment inhibitor characteristics.

Table 3. Nucleoside and Nucleotide Reverse Transcriptase Inhibitors

	Abacavir (Ziagen)	Emtricitabine (Emtriva)	Lamivudine (Epivir)	Zidovudine (ZDV, Retrovir)	Tenofovir Disoproxil Fumarate (Viread)	Tenofovir Alafenamide (Vemlidy)
RTI type	Nucleoside	Nucleoside	Nucleoside	Nucleoside	Nucleotide	Nucleotide
Form	300-mg tablets 20 mg/mL liquid Trizivir: 300 mg ABC/150 mg 3TC/ 300 mg ZDV Triumeq: 600 mg ABC/ 50 mg DTG/ 300 mg 3TC Epzicom (see Lamivudine)	200-mg capsules 10 mg/mL liquid Truvada: 200 mg FTC/300 mg TDF Descovy (200 mg FTC/25 mg TAF) Atripla (see Efavirenz) Complera (see Rilpivirine) Odefsey (see Rilpivirine) Stribild (see Elvitegravir) Genvoya (see Elvitegravir) Biktarvy (see Bictegravir) Symtuza (see Darunavir)	150-, 300-mg tablets 10 mg/mL liquid Combivir: 150 mg 3TC/300 mg ZDV Epzicom: 300 mg 3TC/600 mg ABC Cimduo: 300 mg 3TC/300 mg TDF Dovato (see Dolutegravir) Symfi (see Efavirenz) Trizivir (see Abacavir) Delstrigo (see Doravirine)	100-mg capsules, 300-mg tablets 50 mg/5 mL liquid 10 mg/mL injection	300-mg tablets Truvada: 200 mg FTC/300 mg TDF Cimduo (see Lamivudine) Atripla (see Efavirenz) Complera (see Rilpivirine) Stribild (see Elvitegravir) Delstrigo (see Doravirine)	25-mg tablets Descovy: 200 mg FTC/ 25 mg TAF Odefsey (see Rilpivirine) Genvoya (see Elvitegravir) Biktarvy (see Bictegravir) Symtuza (see Darunavir)
Dosing	300 mg BID or 600 mg daily[a]	200 mg daily or 240 mg liquid daily[b]	150 mg BID or 300 mg daily < 50 kg: 4 mg/kg BID[b]	200 mg TID or 300 mg BID[b]	300 mg daily[c]	25 mg daily[c]; 10 mg daily with cobicistat
Oral bioavailability	82%	93%	86%	60%	40% Take with food	Take with food
Serum half-life (hr)	1.5	10	13–19	1.1	10–14	0.5
Intracellular half-life (hr)	12–26	> 20	18–22	7	> 60	150–180
Elimination	Metabolized by alcohol dehydrogenase and glucuronyltransferase Metabolites; renal	Renal excretion (86%)	Renally excreted unchanged (70%)	Metabolized to ZDV glucuronide (GZDV) Renal excretion of GZDV	Eliminated by renal filtration and active secretion	Eliminated primarily in urine and feces
Adverse drug reactions	Hypersensitivity reaction (including fever, rash, nausea, vomiting, diarrhea, malaise, fatigue, respiratory symptoms – screen for *HLA-B*5701*), increased risk of myocardial infarction	Minimal toxicity; skin hyperpigmentation	Minimal toxicity	Bone marrow suppression, nausea, vomiting, headache, insomnia, asthenia, nail pigmentation, myalgia, lactic acidosis/hepatic steatosis	Diarrhea, nausea, vomiting, headache, loss of bone mineral density, renal toxicity, more favorable effects on lipids than TAF	Diarrhea, nausea, headache, fewer effects on bone mineral density and renal function, more favorable effects on bone and kidneys than TDF
Drug interactions	ABC increases methadone clearance			Myelosuppressive agents Methadone, atovaquone increases ZDV		Carbamazepine, oxcarbazepine, phenytoin, phenobarbital Rifampin, rifabutin, rifapentine St. John's wort

[a]Dosage adjustment in hepatic insufficiency.

[b]Dosage adjustment in renal insufficiency.

[c]Dosage adjustment/avoid use in renal insufficiency: TDF < 50–70 mL/min; TAF < 15 mL/min and not on HD.

ABC = abacavir; BID = twice daily; FTC = emtricitabine; RTI = reverse transcriptase inhibitor; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; 3TC = lamivudine; TID = three times daily; ZDV = zidovudine.

Table 4. Nonnucleoside Reverse Transcriptase Inhibitors

	Doravirine (Pifeltro)	Efavirenz (Sustiva)	Etravirine (Intelence)	Nevirapine (Viramune)	Rilpivirine (Edurant)
Form	100-mg tablets Delstrigo: 300 mg 3TC/ 300 mg TDF/DOR 100 mg	50-, 200-mg capsules 600-mg tablets Atripla: 200 mg FTC/ 300 mg TDF/ EFV 600 mg Symfi: 600 mg EFV/300 mg 3TC/ 300 mg TDF Symfi Lo: 400 mg EFV/300 mg 3TC/300 mg TDF	100-, 200-mg tablets	200-mg tablets 400-mg XR tablets 50 mg/5 mL suspension	25-mg tablets Complera: 200 mg FTC/ 300 mg TDF/RPV 25 mg Odefsey: 200 mg FTC/25 mg TAF/RPV 25 mg Juluca: 25 mg RPV/50 mg DTG Cabenuva (see Cabotegravir)
Dosing	100 mg daily	400–600 mg nightly	200 mg BID	200 mg daily for 14 days, then 200 mg BID or 400 mg daily (XR)[a,b]	25 mg daily
Oral bioavailability	64% Take with or without food	42% Take without food	Take with food	> 90%	Take with food
Serum half-life (hr)	15	40–55	41	25–30	50
Elimination	Metabolized by CYP3A4, 6% excreted in urine	Metabolized by CYP2B6 and CYP3A4; 14%–34% excreted in urine, 16%–61% in feces	Metabolized by CYP3A4, CYP2C9, CYP2C19	Metabolized by CYP3A4; 80% excreted in urine (< 5% unchanged), 10% in feces	Metabolized by CYP3A4
Adverse drug reactions	Rash, nausea, diarrhea, abdominal pain, headache CNS symptoms (fatigue, dizziness, insomnia, abnormal dreams, somnolence) – less than with EFV	Rash, CNS symptoms (insomnia, impaired concentration, nightmares, mania), elevated LFTs, hyperlipidemia	Rash, nausea, hypersensitivity reaction	Rash, GI toxicity, elevated LFTs; hepatotoxicity	Rash, CNS symptoms (depression, insomnia, headache) – less than with EFV
Drug interactions	Avoid CYP3A inducers	Induces CYP3A4 and CYP2B6	Induces CYP3A4 Inhibits CYP2C9 and CYP2C19	Induces CYP3A4 Avoid strong CYP3A inducers and inhibitors	PPIs (contraindicated), histamine-2 blockers, antacids Avoid CYP3A inducers

[a]Dosage adjustment in hepatic insufficiency.

[b]Dosage adjustment in renal insufficiency.

CNS = central nervous system; CYP = cytochrome P450; DOR = doravirine; EFV = efavirenz; ETR = etravirine; LFT = liver function test; NVP = nevirapine; PPI = proton pump inhibitor; RPV = rilpivirine; XR = extended release.

Table 5. Protease Inhibitors

	Atazanavir (Reyataz)	Darunavir (Prezista)	Lopinavir/Ritonavir (Kaletra)	Ritonavir (Norvir)
Form	150-, 200-, 300-mg capsules Evotaz: 300 mg/cobicistat (COBI) 150-mg tablets	75-, 150-, 600-, 800-mg tablets 100 mg/mL solution Prezcobix: 800 mg/COBI 150-mg tablets Symtuza: 800 mg/COBI 150 mg/FTC 200 mg/TAF 10 mg	100/25-, 200/50-mg tablets; 80/20 mg/mL solution	100-mg tablets and oral packet
Dosing	ATV 400 mg daily[a,b] or ATV 300 mg with RTV 100 mg daily or ATV 300 mg with COBI 150 mg daily ATV alone not recommended in antiretroviral-experienced patients If taking TDF but not EFV: ATV 300 mg + RTV 100 mg daily If taking EFV: ATV 400 mg + RTV 100 mg daily	800 mg with RTV 100 mg daily or 600 mg with RTV 100 mg BID[a] DRV 800 mg + COBI 150 mg daily	400/100 mg BID or 800/200 mg daily with food If taking efavirenz or nevirapine: 500 mg/125 mg BID	"Boosting dose" = 100–400 mg divided once or twice daily
Oral bioavailability	Food increases absorption and bioavailability; take with food	Food increases absorption and bioavailability; take with food	Take solution with food; take tablets without respect to food	65%–75%; take with food
Serum half-life (hr)	7	15	56	35
Elimination	CYP3A4	CYP3A4	CYP3A4	CYP3A4 > CYP2D6 > CYP2C9/10
Adverse drug reactions	Indirect hyperbilirubinemia, rash, elevated transaminases, nephrolithiasis, prolonged PR interval and heart block, endocrine disturbances[c]	Rash (sulfa), hepatotoxicity, endocrine disturbances[c]	GI intolerance, fatigue, asthenia, pancreatitis, PR and QTc prolongation, endocrine disturbances[c]	GI intolerance, paresthesias (circumoral and extremities), taste disturbances, asthenia, endocrine disturbances[c]
Drug interactions	Inhibits CYP3A4, PPIs, histamine-2 blockers, antacids Inhaled corticosteroids	Inhibits CYP3A4 Inhaled corticosteroids	Inhibits CYP3A4, CYP2D6 Inhaled corticosteroids	Inhibits CYP3A4, CYP2D6 (potent) Induces glucuronyltransferases Inhaled corticosteroids

[a]Dosage adjustment in hepatic insufficiency.

[b]Dosage adjustment in renal insufficiency.

[c]Endocrine disturbances include insulin resistance (type 2 diabetes in 8%–10%), peripheral fat loss and central fat accumulation (in 50%), and lipid abnormalities (in 70%).

ATV = atazanavir; DRV = darunavir; GI = gastrointestinal; LPV/r = lopinavir/ritonavir; RTV = ritonavir.

Table 6. Integrase Strand Transfer Inhibitors

	Bictegravir	Dolutegravir (Tivicay)	Elvitegravir	Raltegravir (Isentress)	Cabotegravir
Form	Biktarvy: BIC 50 mg/TAF 25 mg/FTC 200 mg	10-, 25-, 50-mg tablets Tivicay PD: 5-mg tablets for oral suspension Triumeq: 600 mg ABC/ 50 mg DTG/300 mg 3TC Dovato: 50 mg DTG/ 300 mg 3TC Juluca (see Rilpivirine)	Stribild: EVG 150 mg/ cobicistat 150 mg/TDF 300 mg/FTC 200 mg Genvoya: Same as Stribild except 10 mg of TAF instead of TDF	25 mg chewable tablets; 100 mg chewable tablets and oral packets; 400 mg tablets; Isentress HD: 600 mg tablets	Cabenuva: 400 mg CAB/ 600 mg RPV, 600 mg CAB/ 900 mg RPV extended release injectable suspension Vocabria: 30 mg tablets Apretude: 600 mg injection
Dosing	50 mg once daily[a,b]	50 mg once daily[a]	Stribild: Once daily[a,b] Genvoya: Once daily[a,b]	400 mg BID Isentress HD: 1200 mg daily	30 mg orally daily for 1 month (optional); then 600/900 IM once, then 400/600 IM monthly OR 600/900 IM monthly x 2 months, then 600/900 every other month
Oral bioavailability	Take with or without food	Take with or without food	Food increases absorption and bioavailability Take with food	Not established	N/A
Serum half-life (hr)	18	14	13	9	5.6-11.5 (CAB)/13-28 (RPV) weeks
Elimination	Metabolized by CYP3A and glucuronidation by UGT1A1	Metabolized by glucuronidation by UGT1A1/3 enzymes and by CYP3A	Metabolized by CYP3A and glucuronidation by UGT1A1/3 enzymes Cobicistat is metabolized by CYP3A and CYP2D6	Metabolized by hepatic glucuronidation by UGT1A1	Metabolized by hepatic glucuronidation by UGT1A1
Adverse drug reactions	Nausea, diarrhea, headache, weight gain Benign increases in creatinine (inhibits creatinine secretion) and bilirubin (blocks bilirubin clearance)	Insomnia, headache, weight gain, hepatotoxicity Benign increases in creatinine (inhibits creatinine secretion) and bilirubin (blocks bilirubin clearance)	Nausea, diarrhea Cobicistat: Benign increases in creatinine (inhibits creatinine secretion) and bilirubin (blocks bilirubin clearance)	Nausea, diarrhea, rash, headache, pyrexia, creatine kinase elevation, insomnia, weight gain Benign increases in creatinine (inhibits creatinine secretion) and bilirubin (blocks bilirubin clearance)	Injection site reactions, fever, fatigue, pain
Drug interactions	Watch CYP3A and UGT1A1 inducers and inhibitors. Avoid rifampin, other rifamycins, St. John's wort, and certain anticonvulsants Dofetilide Divalent and trivalent cations	Inhibitors and inducers of UGT1A3, UGT1A9, BCRP, and P-glycoprotein. Avoid rifampin, rifapentine, certain anticonvulsants, St. John's wort Divalent and trivalent cations Dofetilide	Monitor closely if used with CYP3A inducers or inhibitors. Avoid rifampin, other rifamycins, certain anticonvulsants, St. John's wort Divalent and trivalent cations Inhaled corticosteroids Dofetilide, eplerenone, ivabradine, ranolazine	Inducers of UGT1A1: Rifampin, rifapentine, efavirenz, tipranavir/ ritonavir, certain anticonvulsants Divalent and trivalent cations	Inducers of UGT1A1: Rifampin, rifapentine, efavirenz, tipranavir/ ritonavir, certain anticonvulsants

[a]Dosage adjustment in hepatic insufficiency.

[b]Dosage adjustment in renal insufficiency.

BCRP=breast cancer resistance protein; BIC=bictegravir; CAB=cabotegravir; DTG=dolutegravir; EVG=elvitegravir; RAL=raltegravir; UGT=uridine diphosphate (UDP)-glucuronosyltransferase.

Table 7. Entry Inhibitors

	Enfuvirtide (Fuzeon)	Ibalizumab (Trogarzo)	Lenacapavir (Sulenca)	Maraviroc (Selzentry)	Fostemsavir (Rukobia)
Class	Entry inhibitor	Post-attachment inhibitor	Capsid inhibitor	Entry inhibitor	Attachment inhibitor
Mechanism of action	Attachment of gp120 to CD4 receptor and coreceptors CCR5 or CXCR4 results in exposure of the specific peptide sequence of gp41; enfuvirtide binds to this gp41 peptide sequence, preventing fusion	Blocks HIV from binding to the domain 2 of CD4 and interfering with post-attachment steps required for HIV-1 entry	Directly binds to the interface between capsid protein (p24) subunits in hexamers	Binds to the CCR5 receptor of the CD4 T cell, preventing fusion and HIV entry	Converted to temsavir, which binds to the gp120 subunit of gp160, preventing the virus from interacting with CD4 receptors
Form	90-mg vials	200-mg vials	463.5 mg/1.5 mL vial; 300 mg tablets	150-, 300-mg tablets	600-mg tablets
Dosing	90 mg SC BID	2000 mg IV × 1, followed by 800 mg IV every 2 wk	600 mg orally once and 927 mg subq once, followed by 600 mg orally once 24 hours later, followed by 927 mg subq 2 weeks after first subq injection, then every 6 months after that	150–600 mg BID (depending on concomitant drug interactions)[a]	600 mg BID
Oral bioavailability	N/A	N/A	6%-10% orally; 100% subq	23%–33%	27%
Serum half-life (hr)	3.8	64	10-12 d oral; 8-12 weeks subq	14–18	11
Elimination	Metabolized by hydrolysis			Metabolized by CYP3A	Metabolized by esterases and CYP3A4
Adverse drug reactions	Hypersensitivity reactions, local injection site reactions (98%), pneumonia	Diarrhea, dizziness, nausea, rash, elevations in bilirubin, creatinine, glucose, and lipase, blood dyscrasias	injection site reaction (65%), increased serum creatinine (13%)	Abdominal pain, cough, dizziness, musculoskeletal symptoms, pyrexia, rash, upper respiratory tract infections, hepatotoxicity, orthostatic hypotension	Nausea, diarrhea, abdominal pain, headache, fatigue, rash, sleep disturbances, elevations in LFTs and creatinine, may prolong QTc
Drug interactions	None	None	CYP 3A4 substrate, Pgp, UGT1A1	CYP3A substrate (watch CYP3A inducers and inhibitors)	CYP3A4 substrate (watch CYP3A4 inducers and inhibitors)

[a]Dosage adjustment in renal insufficiency.

FTR = fostemsavir; gp = glycoprotein; IBA = ibalizumab; IV = intravenous(ly); MVC = maraviroc; N/A = not applicable; SC = subcutaneous(ly); T20 = enfuvirtide.

Patient Case

1. F.G. is a 27-year-old man who is HIV positive but asymptomatic. His CD4 count is 550 cells/mm^3, and his viral load is 5000 copies/mL by reverse transcriptase polymerase chain reaction. Which is the best treatment for F.G.?

   A. ART should not be given because his CD4 count is still above 500 cells/mm^3.

   B. Initiate emtricitabine/tenofovir only because his CD4 count is still above 500 cells/mm^3.

   C. Initiate combination therapy of abacavir, lamivudine, and atazanavir/ritonavir.

   D. Initiate combination therapy of tenofovir, emtricitabine, and dolutegravir.

5. Treatment of the patient who is HIV positive
   a. Guidelines recommend HIV treatment for all infected patients, regardless of CD4 count (AI).
   b. Recommended initial regimens for most patients with HIV: The optimal ART for a treatment-naive patient consists of two NRTIs in combination with an INSTI.
      i. Bictegravir/tenofovir alafenamide/emtricitabine
      ii. Dolutegravir/abacavir/lamivudine; only for patients who are *HLA-B*5701* negative
      iii. Dolutegravir plus tenofovir/emtricitabine
      iv. Dolutegravir plus lamivudine; except for individuals with HIV RNA >500,000 copies/mL, HBV coinfection, or when ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available
   c. Recommended initial regimens in certain clinical situations:
      i. NNRTI-based regimens
         (a) Doravirine/tenofovir disoproxil fumarate/lamivudine or doravirine plus tenofovir alafenamide/emtricitabine
         (b) Efavirenz/tenofovir/emtricitabine
         (c) Rilpivirine/tenofovir/emtricitabine; only for patients with viral load less than 100,000 copies/mL and CD4 count greater than 200 cells/mm^3
      ii. PI-based regimens (in general, darunavir preferred over atazanavir)
         (a) Atazanavir/ritonavir or atazanavir/cobicistat plus tenofovir/emtricitabine; if TDF, not recommended for CrCl less than 70 mL/minute/1.73 m^2
         (b) Darunavir/ritonavir or darunavir/cobicistat plus abacavir/lamivudine; only for patients who are *HLA-B*5701* negative
         (c) Darunavir/ritonavir or darunavir/cobicistat plus tenofovir/emtricitabine; if TDF, not recommended for CrCl less than 70 mL/minute/1.73 m^2. For people with HIV who do not have a history of using long-acting cabotegravir (CAB-LA) as pre-exposure prophylaxis (PrEP)
      iii INSTI-based regimens:
         (a) Elvitegravir/cobicistat/tenofovir/emtricitabine
            (1) Only for patients with pre-ART CrCl greater than 70 mL/minute/1.73 m^2 if using TDF or greater than 30 mL/minute/1.73 m^2 if using TAF
         (b) Raltegravir plus tenofovir/emtricitabine
      iv. Regimens to consider when ABC, TAF and TDF cannot be used:
         (a) Dolutegravir plus lamivudine (see criteria for this regimen listed above)
         (b) Darunavir/ritonavir plus raltegravir (only if HIV RNA less than 100,000 copies/mL and CD4 greater than 200/mm^3);
         (c) Darunavir/ritonavir plus lamivudine

Patient Case

2. Six months after F.G. (from patient case 1) starts appropriate therapy, his CD4 count is 720 cells/mm^3, and his viral load is undetectable. Two years later, his CD4 count decreases to 310 cells/mm^3, and his viral load is 15,000 copies/mL. Resistance testing detects resistance to dolutegravir. His HIV regimen is changed to abacavir, lamivudine, and darunavir/ritonavir. Which of the following tests must be performed before starting abacavir?
   A. Liver function tests because of the risk of hepatotoxicity.
   B. *HLA-B*5701* allele screening because of the risk of a serious hypersensitivity reaction.
   C. Hemoglobin A1C and a lipid panel because of the risk of endocrine disturbances.
   D. Bilirubin because of the risk of hyperbilirubinemia.

II. OPPORTUNISTIC INFECTIONS: PATIENTS WITH HIV

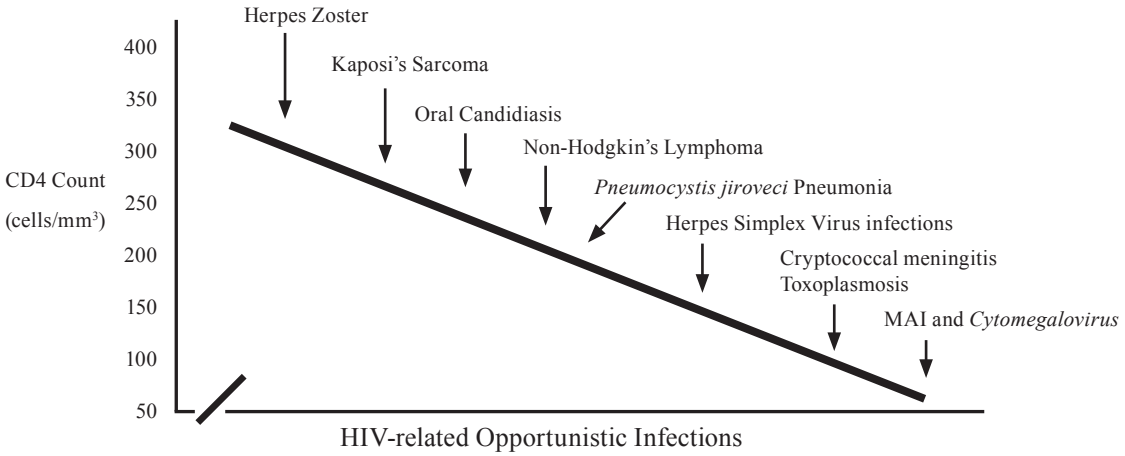


Figure 3. Relationship between CD4 count and risk of HIV-related opportunistic infections.
MAI = *Mycobacterium avium-intracellulare.*

A. Initiating Potent Combination ART in the Setting of Acute Opportunistic Infections
   1. Opportunistic infections with no effective therapy require prompt initiation of ART: cryptosporidiosis, microsporidiosis, promyelocytic leukemia, and Kaposi sarcoma.
   2. ART should begin within 2 weeks of acute opportunistic infections, except for tuberculosis (TB) meningitis, in which therapy should begin within 2 weeks when the CD4 count is less than 50 cells/mm^3 and close monitoring of toxicities and neurological events is possible, and by 8 weeks for all others, and cryptococcal meningitis, in which therapy should begin 4−6 weeks after diagnosis (because of immune reconstitution inflammatory syndrome [IRIS]).

B. *Pneumocystis jiroveci* Pneumonia (PJP)
   1. Clinical presentation
      a. Fever, shortness of breath, and nonproductive cough
      b. Elevated lactate dehydrogenase
      c. Diffuse pulmonary infiltrates
      d. In general, with CD4 counts less than 200 cells/mm^3
      e. Hypoxemia with elevated alveolar-arterial (A-a) gradient and decreased P_{O_2}; A-a gradient = 150 − P_{O_2} − P_{CO_2}

Patient Cases

3. Three years later, F.G. (from patient cases 1–2) has not responded to any of his ART regimens because of resistance or intolerance. His CD4 count has decreased to 135 cells/mm^3. For which infection is it most important that F.G. receive primary prophylaxis?
   A. *Pneumocystis jiroveci* pneumonia (PJP).
   B. Cryptococcal meningitis.
   C. Cytomegalovirus (CMV).
   D. *Mycobacterium avium* complex (MAC).

4. B.L. is a 44-year-old HIV-positive man who arrives at the emergency department severely short of breath. He is an extremely nonadherent patient and has not seen a health care provider in more than 3 years. A chest radiograph shows pulmonary infiltrates in both lung fields. The results of the laboratory tests are as follows: sodium 147 mEq/L, potassium 4.2 mEq/L, chloride 104 mEq/L, bicarbonate 25.2 mEq/L, glucose 107 mg/dL, blood urea nitrogen 38 mg/dL, serum creatinine 1.1 mg/dL, aspartate aminotransferase 28 IU/L, alanine aminotransferase 32 IU/L, lactate dehydrogenase 386 IU/L, alkaline phosphate 75 IU/L, pH 7.45, P_{O_2} 63 mm Hg, P_{CO_2} 32 mm Hg, and oxygen saturation 85%. His CD4 count is 98 cells/mm^3. Sputum Gram stain is negative, as is silver stain. Which is the best therapy for B.L.?
   A. Pentamidine intravenously with adjuvant prednisone therapy for 21 days.
   B. Trimethoprim/sulfamethoxazole orally for 21 days.
   C. Trimethoprim/sulfamethoxazole intravenously with adjuvant prednisone therapy for 21 days.
   D. Atovaquone orally for 21 days.

2. Diagnosis
   a. Induced sputum, bronchoalveolar lavage, or transbronchial biopsy
   b. Methenamine silver stain of sputum sample
3. Therapy
   a. Trimethoprim/sulfamethoxazole (preferred)
      i. Dose: 15–20 mg/kg/day of trimethoprim divided every 6–8 hours for 21 days (intravenously for moderate to severe PJP); trimethoprim/sulfamethoxazole double strength 2 tablets three times daily or weight based (for mild to moderate PJP)
      ii. Adverse effects (80% of patients, with 20%–60% requiring discontinuation)
         (a) Nausea and vomiting
         (b) Rash
         (c) Anemia, thrombocytopenia, leucopenia
         (d) Renal impairment or hyperkalemia (small increases in serum creatinine occur because of competition between trimethoprim and creatinine for renal secretion)
      iii. Prophylactic dose
         (a) Preferred: Trimethoprim/sulfamethoxazole double strength or single strength once daily (pediatric dose, 150 mg/m^2 per dose of trimethoprim and 750 mg/m^2 per dose of sulfamethoxazole)
         (b) Alternative: Trimethoprim/sulfamethoxazole double strength three times/week
   b. Clindamycin and primaquine (alternative)
      i. Dose: Clindamycin 600 mg every 6 hours or 900 mg every 8 hours intravenously plus primaquine 30 mg daily (for moderate to severe disease) or 450 mg every 6 hours or 600 mg every 8 hours orally and primaquine base 30 mg/day for 21 days (for mild to moderate disease)

ii. Adverse effects
(a) Rash
(b) Anemia, methemoglobinemia (test for glycose-6-phosphate dehydrogenase [G6PD] deficiency)
(c) Diarrhea

c. Atovaquone (Mepron) (alternative)
i. Dose: 750 mg twice daily for 21 days given with a high-fat meal (only for mild to moderate PJP)
ii. Pediatric dose (less than 40 kg) = 40 mg/kg/day divided twice daily
iii. Equal to trimethoprim/sulfamethoxazole for PJP but not an antibacterial
iv. Potential for decreased efficacy in patients with diarrhea (because of poor absorption)
v. Adverse effects
(a) Nausea and vomiting
(b) Rash
(c) Transient increase in liver function tests
(d) Insomnia, headache, fever
vi. Prophylactic dose = 1500 mg once daily
(a) Preferred alternative prophylactic regimen based on safety, tolerability, and efficacy

d. Pentamidine (alternative)
i. Dose: 4 mg/kg/day intravenously for 21 days (for moderate to severe disease)
ii. Adverse effects
(a) Hypotension
(b) Rash
(c) Electrolyte disturbances
(d) Hypoglycemia or hyperglycemia
(e) Pancreatitis
iii. Prophylactic dose for patients with immunocompromising conditions: 300 mg by nebulization (Respirgard) once monthly (can predose with β-agonist to diminish respiratory irritation)

e. Trimethoprim and dapsone (alternative)
i. Dose: 15 mg/kg/day of trimethoprim divided every 8 hours and dapsone 100 mg/day for 21 days (only for mild to moderate PJP)
ii. Adverse effects
(a) Nausea and vomiting
(b) Anemia (test for G6PD deficiency)
iii. Prophylactic dose: Dapsone 100 mg/day (pediatric dose, 2 mg/kg/day) alone or 50 mg/day or 200 mg/week with 50–75 mg of pyrimethamine and 25 mg of leucovorin weekly

f. Adjuvant therapy: Corticosteroids
i. Used in patients with severe PJP (A-a gradient of 35 or more or Po_2 of 70 mm Hg or less); start within 72 hours
ii. Decreases mortality
iii. Dose: 40 mg twice daily of prednisone for 5 days, followed by 40 mg/day for 5 days, then 20 mg/day for remainder of PJP therapy

4. Prophylaxis
a. Secondary prophylaxis in patients after PJP (may be discontinued if CD4 count is more than 200 cells/mm^3 for 3 months or longer because of potent combination ART)
b. Primary prophylaxis in patients with CD4 count less than 200 cells/mm^3 (may be discontinued if CD4 count is more than 200 cells/mm^3 for 3 months or longer because of potent combination ART)
c. Consider stopping primary or secondary prophylaxis in patients with CD4 counts of 100-200 cells/mm^3 if HIV plasma RNA level is below limits of detection for at least 3-6 months.

C. Toxoplasmosis
   1. Description
      a. *Toxoplasma gondii* (protozoan)
      b. Felines are the hosts for sporozoite production. To decrease risk change litter box daily, wash hands after changing litter box or have someone else change the litter box, and, ideally, keep the cat indoors.
      c. From 15% to 68% of adults in the United States are seropositive for *T. gondii*.
      d. Secondary to undercooked beef, lamb, pork, or raw shellfish (stress avoidance in patients with HIV)
      e. Case-defining illness in 2.1% of patients with AIDS
   2. Signs and symptoms
      a. Fever, headache, altered mental status
      b. Focal neurologic deficits (60%): Hemiparesis, aphasia, ataxia, visual field loss, nerve palsies
      c. Seizures (33%)
      d. CSF: Mild pleocytosis, increased protein, normal glucose
   3. Diagnosis
      a. Brain biopsy: Only definitive diagnosis but generally reserved for patients who do not respond to specific therapy or when other workup suggests an etiology other than toxoplasmosis
      b. Antibodies or *T. gondii* isolation in serum or CSF
      c. Magnetic resonance imaging scan or computed tomographic scan: Multiple, bilateral, hypodense, ring-enhancing mass lesions (magnetic resonance imaging scan more sensitive than computed tomographic scan)
   4. Therapy
      a. Preferred therapy
         i. Pyrimethamine 50–75 mg/day (loading dose of 200 mg) *plus*
         ii. Sulfadiazine 1000–1500 mg every 6 hours (watch crystalluria)
            (a) Bone marrow suppression: Thrombocytopenia, granulocytopenia, anemia
            (b) Add folinic acid (leucovorin) 10-25 mg/day to reduce bone marrow–suppressive effects of pyrimethamine.
            (c) Duration: at least 6 weeks and after signs and symptoms resolve
      b. Alternative therapy
         i. Clindamycin 600 mg intravenously or orally every 6 hours plus pyrimethamine (see above) – Use for sulfa intolerance or nonresponse to preferred therapy
         ii. Trimethoprim/sulfamethoxazole 5 mg/kg of trimethoprim intravenously or orally twice daily
         iii. Atovaquone 1500 mg orally twice daily plus pyrimethamine/leucovorin (see above)
         iv. Atovaquone 1500 mg orally twice daily plus sulfadiazine (see above)
         v. Atovaquone 1500 mg orally twice daily
   5. Prophylaxis
      a. Relapse rates approach 80% without maintenance therapy.
      b. Toxoplasma-seropositive patients with a CD4 count of 100 cells/mm^3 or less should receive primary prophylaxis.
      c. Primary prophylaxis
         i. Trimethoprim/sulfamethoxazole double strength once daily or dapsone/pyrimethamine/leucovorin or atovaquone with or without pyrimethamine at doses used for PJP prophylaxis
         ii. May be discontinued if the CD4 count is more than 200 cells/mm^3 for 3 months or longer because of potent combination ART
         iii. Consider stopping primary prophylaxis in patients with CD4 counts of 100-200 cells/mm^3 if HIV plasma RNA level is below limits of detection for at least 3-6 months.

d. Chronic maintenance therapy
    i. Pyrimethamine 25–50 mg/day plus leucovorin 10–25 mg/day with sulfadiazine 2–4 g/day
    ii. Clindamycin 600 mg orally every 8 hours plus pyrimethamine (see above) – Use for sulfa intolerance or non-response to preferred therapy.
    iii. Trimethoprim/sulfamethoxazole double strength orally twice daily or daily
    iv. Atovaquone 750–1500 mg orally twice daily plus pyrimethamine/leucovorin (see above)
    v. Atovaquone 750–1500 mg orally twice daily plus sulfadiazine (see above)
    vi. Atovaquone 750–1500 mg orally twice daily
    vii. May be discontinued if the CD4 count is more than 200 cells/mm^3 and patient is asymptomatic for 6 months or longer because of potent combination ART

D. *Candida* Infections
1. Oral *Candida* infections (thrush)
    a. More than 90% of patients with AIDS sometime during their illness
    b. Signs and symptoms
        i. Creamy white, curdlike patches on the tongue and other oral mucosal surfaces
        ii. Pain, decreased food and fluid intake
2. *Candida* esophagitis
    a. Not always an extension of oral thrush (30% do not have oral thrush)
    b. Signs and symptoms: Painful swallowing, obstructed swallowing, substernal pain
3. Diagnosis
    a. Signs and symptoms of infection
    b. Fungal cultures, potassium hydroxide smear
    c. Endoscopic evaluation
4. Therapy
    a. Oropharyngeal candidiasis (treat 7–14 days)
        i. Fluconazole 100 mg orally daily
        ii. Alternative: Itraconazole solution 200 mg orally daily or posaconazole suspension 400 mg orally daily (after twice daily on day 1) or miconazole buccal tablets 50 mg orally daily or clotrimazole troches 10 mg orally five times daily or nystatin 5 mL (100,000 units/mL): swish and swallow four or five times daily
    b. Esophageal candidiasis (treat 14–21 days)
        i. Fluconazole 100–400 mg orally or intravenously daily or itraconazole solution 200 mg orally daily
        ii. Alternative: Voriconazole, caspofungin, micafungin, anidulafungin, amphotericin B deoxycholate, lipid formulation of amphotericin B, posaconazole or isavuconazole
    c. Vulvovaginal candidiasis
        i. Fluconazole 150 mg orally for one dose or topical azoles for 3–7 days
        ii. Alternative: Itraconazole solution 200 mg orally daily for 3–7 days

E. Cryptococcosis
1. *Cryptococcus neoformans*
2. Occurs in 6%–10% of patients with AIDS
3. In general, occurs in patients with CD4 counts less than 50 cells/mm^3
4. Acute mortality is 10%–25%, and 12-month mortality is 30%–60%.
5. Worldwide distribution
    a. Found in aged pigeon droppings and nesting places (e.g., barns, window ledges)
    b. Organism must be aerosolized and inhaled; it then disseminates hematogenously.

Patient Cases

5. G.H. is a 33-year-old HIV-positive man who presents to the clinic with a severe headache that has gradually worsened during the past 3 weeks. He also has memory problems and is always tired. He has refused ART in the past, and his most recent CD4 count was 75 cells/mm^3. He is given a diagnosis of cryptococcal meningitis. Which is the best treatment for G.H.?
   A. Amphotericin B deoxycholate 0.7–1 mg/kg/day plus fluconazole 800 mg daily for 2 weeks, followed by fluconazole 400 mg/day for 8 weeks. Begin ART in the first 1–2 weeks of therapy.
   B. Liposomal amphotericin B 3–4 mg/kg/day plus flucytosine 25 mg/kg every 6 hours for 2 weeks, followed by fluconazole 800 mg/day for 8 weeks. Begin ART after 4–6 weeks of antifungal therapy.
   C. Fluconazole 1200 mg/day for 10–12 weeks, followed by fluconazole 800 mg/day for 8 weeks. Begin ART after 4–6 weeks of antifungal therapy.
   D. Lipid-formulated amphotericin B 3–4 mg/kg/day plus fluconazole 800 mg/day for 2 weeks, followed by fluconazole 400 mg/day for 8 weeks. Begin ART in the first 1-2 weeks of therapy.

6. After completing induction and consolidation treatment for cryptococcal meningitis, G.H. is initiated on potent combination ART. For 2, 6, and 8 months after starting the therapy, his CD4 counts are 212, 344, and 484 cells/mm^3, respectively. Which is the best follow-up therapy for G.H. now?
   A. Continue fluconazole maintenance therapy for 4 months, then it can be discontinued, because ART will have been initiated for 1 year.
   B. Continue maintenance therapy with fluconazole for at least 1 year; then, it can be discontinued because the CD4 counts have increased.
   C. Continue maintenance therapy with fluconazole until CD4 counts are greater than 500 cells/mm^3.
   D. Discontinue maintenance therapy with fluconazole.

6. Signs and symptoms
   a. Almost always meningitis (66%–84%)
   b. Usually present for weeks or months (1 day to 4 months; average 31 days)
   c. Insidious onset
      i. Low-grade fever (80%–90%)
      ii. Headaches (80%–90%)
      iii. Altered sensorium (20%): Irritability, somnolence, clumsiness, impaired memory and judgment, behavioral changes
      iv. Seizures may occur late in the course (less than 10%).
      v. Minimal nuchal rigidity, meningismus, photophobia
7. Diagnosis
   a. Cerebrospinal fluid (CSF) changes including:
      i. Positive CSF cultures
      ii. CSF cryptococcal antigen titer (91%)
      iii. Elevated opening pressure greater than 20 cm H_2O
   b. Serum cryptococal antigen greater than 1:160 via lateral flow assay (LFA) indicates disseminated disease
8. Induction therapy (duration: 2 weeks)
   a. Preferred:
      i. Liposomal amphotericin B 3–4 mg/kg/day plus flucytosine 25 mg/kg every 6 hours
      ii. Amphotericin B deoxycholate 0.7–1 mg/kg/day plus flucytosine 25 mg/kg every 6 hours (only if cost is an issue and the risk of renal dysfunction is low)

b. Alternatives:
   i. Amphotericin B lipid complex 5 mg/kg/day plus flucytosine 25 mg/kg every 6 hours
   ii. Liposomal amphotericin B 3–4 mg/kg/day plus fluconazole 800–1200 mg/day
   iii. Amphotericin B deoxycholate 0.7–1 mg/kg/day plus fluconazole 800–1200 mg/day
   iv. Liposomal amphotericin B 3–4 mg/kg/day alone
   v. Fluconazole 800–1200 mg/day plus flucytosine 25 mg/kg every 6 hours
   vi. Fluconazole 1200 mg/day alone
   vii. Amphotericin B deoxycholate 0.7–1.0 mg/kg/day alone
   viii. Liposomal amphotericin B 3–4 mg/kg/day plus flucytosine 25 mg/kg every 6 hours for 1 week, followed by fluconazole 1200 mg/day
   ix. Liposomal amphotericin B 10 mg/kg once plus flucytosine 25 mg/kg every 6 hours plus fluconazole 1200 mg/day

9. Consolidation therapy (duration: at least 8 weeks, beginning after induction therapy)
   a. Fluconazole 800 mg daily (dose can be decreased to 400 mg daily if CSF is negative and ART is started)
10. Maintenance therapy – Preferred: Fluconazole 200 mg/day for at least 1 year
11. Outcome
   a. Delay initiating combination ART in patients with cryptococcal meningitis for 2–10 weeks because of the risk of IRIS.
   b. Therapeutic response: 42%–75%
   c. Relapse: 50%–90% (with about 100% mortality)
12. Prophylaxis
   a. Relapses usually occur within first year after therapy (less often with potent combination ART).
   b. Secondary prophylaxis: Fluconazole 200 mg/day (may consider discontinuing after a minimum of 1 year of chronic maintenance therapy if CD4 count is more than 100 cells/mm^3 for 3 months or longer with suppressed HIV RNA and potent combination ART and patient remains asymptomatic; reinitiate if CD4 count decreases to less than 100 cells/mm^3)
   c. Primary prophylaxis: Not indicated (decreases the incidence of cryptococcosis but does not decrease mortality and may lead to resistance)

Patient Case

7. J.C. is a 36-year-old HIV-positive woman with severe anemia. She has been tested for iron deficiency and has been taken off zidovudine and trimethoprim/sulfamethoxazole. She has also started to lose weight and to have severe diarrhea. A blood culture is positive for *Mycobacterium avium-intracellulare* (MAI). Which treatment is best for J.C.?

   A. Clarithromycin plus ethambutol for 2 weeks, followed by maintenance with clarithromycin alone.

   B. Azithromycin plus ethambutol for at least 12 months.

   C. Clarithromycin plus isoniazid for 2 weeks, followed by maintenance with clarithromycin alone.

   D. Ethambutol plus rifabutin indefinitely.

F. *Mycobacterium avium* Complex (MAC)
   1. Organism characteristics
      a. Complex is similar (main species are *M. avium* and *Mycobacterium intracellulare,* which are not differentiated microbiologically).
      b. Ubiquitous in soil and water and are transmitted through inhalation, ingestion, or inoculation by the respiratory or gastrointestinal (GI) tract
      c. Usually occurs in patients with HIV having a CD4 count less than 50 cells/mm^3
      d. MAC is independently associated with risk of death, and treatment prolongs survival.

2. Signs and symptoms (nonspecific)
    a. Weight loss, intermittent fevers, chills, night sweats, abdominal pain, diarrhea, chronic malabsorption, and progressive weakness
    b. Anemia
    c. Elevated alkaline phosphatase
3. Diagnosis
    a. Blood or lymph node culture
    b. Bone marrow biopsy
    c. Stool cultures (do not treat if cultured only in the stool)
4. Therapy
    a. Preferred therapeutic regimen is macrolide plus ethambutol: Clarithromycin 500 mg (7.5–15 mg/kg) twice daily *or* azithromycin 500–600 mg/day (10–20 mg/kg) if drug interactions or intolerance to clarithromycin, plus ethambutol 15 mg/kg/day for a minimum of 12 months
    b. Other agents: Consider adding to preferred therapy if advanced immunosuppression (CD4 count less than 50 cells/mm^3), high mycobacterial loads (more than 2 log CFU/mL of blood), or in the absence of effective ART.
        i. Rifabutin (Mycobutin) 300 mg/day (rifabutin dose chosen on the basis of other antiretrovirals because of drug-drug interactions)
        ii. A fluoroquinolone such as levofloxacin 500 mg oral daily or moxifloxacin 400 mg oral daily
        iii. An aminoglycoside such as amikacin 10–15 mg/kg intravenously daily or streptomycin 1 g intravenously or intramuscularly daily
    c. Chronic maintenance therapy or secondary prophylaxis may be discontinued after 12 months of therapy if CD4 count is more than 100 cells/mm^3 for 6 months or longer because of potent combination ART and if patient is asymptomatic. Restart if CD4 count drops below 100 cells/mm^3.
5. Primary prophylaxis in patients with CD4 counts less than 50 cells/mm^3 who are not receiving ART or who have viremia on current ART (may be discontinued upon initiation of effective ART); primary prophylaxis not recommended if patients are immediately initiated on ART
    a. Clarithromycin 500 mg orally twice daily: Lower incidence of MAC bacteremia (vs. placebo)
    b. Azithromycin 1200 mg orally once weekly
    c. Azithromycin 600 mg orally twice weekly
    d. Alternative: Rifabutin 300 mg/day (150 mg orally twice daily with food if there are GI adverse effects)

G. Cytomegalovirus (CMV)
1. Characteristics of CMV infection
    a. Fifty-three percent of Americans age 18–25 years are CMV positive.
    b. Eighty-one percent of Americans older than 35 years are CMV positive.
    c. More than 95% of men who have sex with men are CMV positive.
    d. About 90% of CMV infections are asymptomatic (if illness occurs, it resembles mononucleosis).
    e. Virus remains latent in the host after initial infection but may reactivate if patient becomes immunocompromised (especially cell-mediated immunity).
2. Diagnosis of CMV infection is usually made on the basis of clinical manifestations
3. Manifestations of CMV
    a. Retinitis
        i. Occurs in 10%–15% of patients with AIDS; is the clinically most important CMV infection
        ii. In general, patients have CD4 counts less than 50 cells/mm^3 and high plasma HIV RNA concentrations.
        iii. Begins unilaterally and spreads bilaterally
        iv. Early complaints: "Floaters," pain behind the eye
        v. In general, progressive; no spontaneous resolution (blindness in weeks to months)
        vi. Rate of progression is 26%, even with treatment; retinal detachment very common

b. Other manifestations
    i. Esophagitis or colitis
    ii. Pneumonitis
    iii. Neurologic
4. Therapy for CMV infections
    a. CMV retinitis
        i. Sight-threatening lesions
            (a) Valganciclovir 900 mg orally twice daily for 14–21 days, followed by 900 mg orally daily, with or without intravitreal injections of ganciclovir or foscarnet for 1–4 doses over a period of 7–10 days
            (b) Alternative therapy (all regimens include intravitreal injections as listed above):
                (1) Ganciclovir 5 mg/kg intravenously every 12 hours for 14–21 days, followed by ganciclovir 5 mg/kg intravenously daily or valganciclovir 900 mg orally daily
                (2) Foscarnet 60 mg/kg intravenously every 8 hours or 90 mg/kg intravenously every 12 hours for 14–21 days, then 90–120 mg/kg intravenously daily
                (3) Cidofovir 5 mg/kg weekly intravenously for 2 weeks; then 5 mg/kg every other week with saline hydration and probenecid
        ii. Peripheral lesions
            (a) Valganciclovir 900 mg orally twice daily for 14–21 days, followed by 900 mg orally daily for the first 3–6 months until ART-induced immune recovery.
    b. Other CMV infections
        i. Esophagitis or colitis
            (a) Ganciclovir 5 mg/kg intravenously every 12 hours, followed by valganciclovir 900 mg orally twice daily when tolerated
            (b) Alternative therapy:
                (1) Foscarnet 60 mg/kg intravenously every 8 hours or 90 mg/kg intravenously every 12 hours
                (2) Valganciclovir 900 mg orally twice daily (if tolerable)
        ii. Pneumonitis – Use ganciclovir or foscarnet at retinitis doses.
        iii. Neurologic – Combination of ganciclovir and foscarnet at retinitis doses
5. Consider waiting up to 2 weeks after initiating CMV therapy to start ART in a treatment-naive patient
6. Chronic maintenance therapy
    a. Recommended for patients with CMV retinitis (see individual drugs for specific doses); do not discontinue therapy without consultation with an ophthalmologist, treatment duration for 3–6 months, lesions are inactive, and CD4+ count greater than 100 cells/mm^3 for 3–6 months in response to ART.
    b. Primary prophylaxis not recommended. In patients with CD4 counts less than 50 cells/mm^3, regular funduscopic examinations are recommended.

III. TUBERCULOSIS (TB)

A. *Mycobacterium tuberculosis*
1. Factors associated with acquiring TB
    a. Exposure to people with active pulmonary TB
    b. Geographic location
    c. Low socioeconomic status
    d. Nonwhite race
    e. Male sex
    f. HIV infection
    g. Foreign birth

2. Epidemiology (Figure 4)

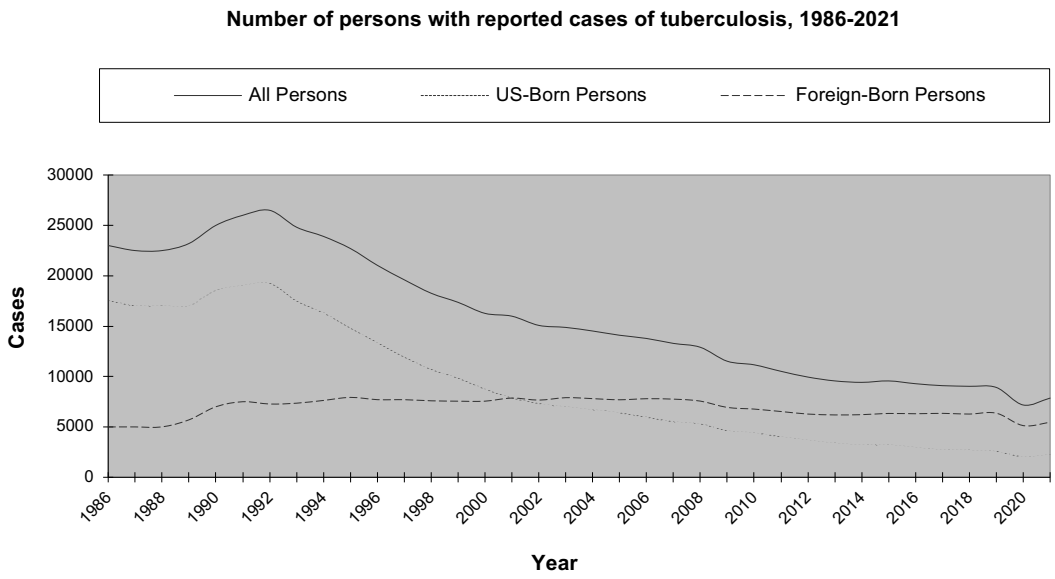


Figure 4. Epidemiology of tuberculosis.

B. Pathophysiology (Figure 5)
   1. Person-to-person transmission: Airborne droplets carrying *M. tuberculosis* are inhaled.
   2. Infection primarily pulmonary but can occur in other organ systems

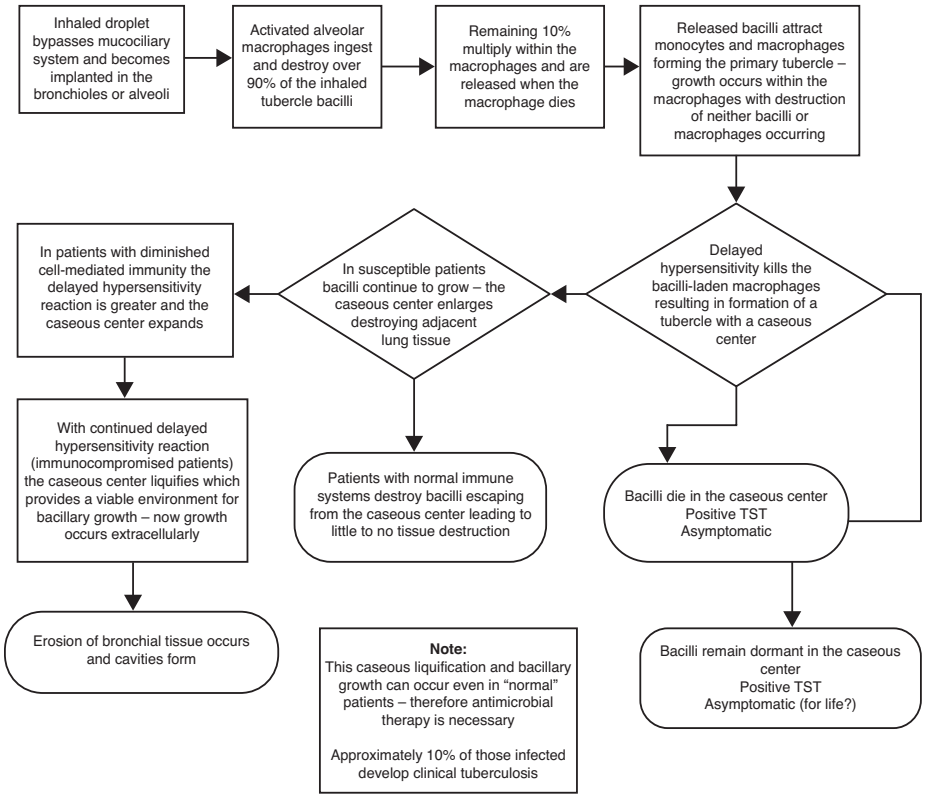

Inhaled droplet bypasses mucociliary system and becomes implanted in the bronchioles or alveoli
Activated alveolar macrophages ingest and destroy over 90% of the inhaled tubercle bacilli
Remaining 10% multiply within the macrophages and are released when the macrophage dies
Released bacilli attract monocytes and macrophages forming the primary tubercle – growth occurs within the macrophages with destruction of neither bacilli or macrophages occurring
Delayed hypersensitivity kills the bacilli-laden macrophages resulting in formation of a tubercle with a caseous center
In susceptible patients bacilli continue to grow – the caseous center enlarges destroying adjacent lung tissue
In patients with diminished cell-mediated immunity the delayed hypersensitivity reaction is greater and the caseous center expands
With continued delayed hypersensitivity reaction (immunocompromised patients) the caseous center liquifies which provides a viable environment for bacillary growth – now growth occurs extracellularly
Erosion of bronchial tissue occurs and cavities form
Patients with normal immune systems destroy bacilli escaping from the caseous center leading to little to no tissue destruction
Bacilli die in the caseous center
Positive TST
Asymptomatic
Bacilli remain dormant in the caseous center
Positive TST
Asymptomatic (for life?)
Note:
This caseous liquification and bacillary growth can occur even in "normal" patients – therefore antimicrobial therapy is necessary
Approximately 10% of those infected develop clinical tuberculosis

Figure 5. Pathophysiology of tuberculosis.
TST = tuberculin skin test

C. Diagnosis (Table 8)

Table 8. Diagnosis of Tuberculosis

Nonspecific Signs and Symptoms	Radiology	Microbiology
Cough Malaise Weight loss Fever, chills Night sweats Pleuritic pain	Chest radiograph: patchy or nodular infiltrates in upper lobes; cavitary lesions	Sputum smear for AFB Sputum culture for *Mycobacterium tuberculosis* Rapid detection through PCR probe

AFB = acid-fast bacillus; PCR = polymerase chain reaction.

Patient Case

8. J.M. is a 42-year-old man who works at a long-term care facility and was recently exposed to a patient with TB; he was not wearing personal protective equipment. A TST is placed, and 48 hours later, he has an 18-mm induration. This is the first time he has reacted to this test. His chest radiograph is negative. Which is best in view of J.M.'s positive TST?

   A. No treatment is necessary, and J.M. should have another TST in 8–10 weeks.

   B. J.M. should have another TST in 1 week to see whether this is a booster effect.

   C. J.M. should be monitored closely, but no treatment is necessary because he is older than 35 years.

   D. J.M. should be initiated on rifampin 600 mg/day plus isoniazid 300 mg/day for 3 months.

1. Tuberculin skin test (TST) (Table 9)
   a. Recommended dose is 5 tuberculin units/0.1 mL.
   b. Mantoux method
      i. Intradermal injection of tuberculin into forearm
      ii. Measure diameter of induration after 48–72 hours.
   c. False-negative tests occur in 15%–20% of people infected with *M. tuberculosis,* primarily in those recently infected or anergic.
   d. Only 8% of people vaccinated with Bacille Calmette-Guérin (BCG) at birth will react 15 years later.
2. Interferon-gamma release assays (IGRA)
   a. QuantiFERON-TB Gold and T-SPOT.TB
   b. Blood test that detects the release of interferon gamma in response to *M. tuberculosis* infection
   c. Less sensitivity but greater specificity than the TST for predicting future active infection
3. Booster effect
   a. The TB test can restimulate hypersensitivity in those exposed in the past.
   b. Occurs within 1 week of the test and persists for more than 1 year
   c. Those with negative TST reactions can be retested in 1 week; if positive, result should be attributed to boosting of a subclinical hypersensitivity; chemoprophylaxis is not necessary.
4. TB screening of health care workers
   a. Baseline screening when starting employment (TST or IGRA)
   b. If baseline screening positive and health care worker is asymptomatic and unlikely infected, repeat.
   c. If repeat screening is positive, treat for latent TB.
   d. No need for annual screening after baseline.
   e. Recheck TST or IGRA after known TB exposure.

Table 9. Testing for Latent Tuberculosis Infection

Likelihood of Infection with M. tuberculosis (see below)	Risk of Progressing to Tuberculosis if Infected (see below)	Criterion for Positive Skin Test (mm)	Recommended testing*
Likely	Low to intermediate	≥ 10	IGRA recommended if history of BCG vaccine or unlikely to return to have TST read (otherwise IGRA suggested) TST is acceptable alternative
Likely	High	≥ 5	IGRA or TST (data insufficient to recommend one over the other)
Unlikely	Low to high	≥ 15	Do not test with either IGRA or TST (may be done for employee health surveillance)

Groups with increased likelihood to be infected (i.e., "likely")	**Risk of Developing Tuberculosis**
• Household contact or recent exposure of an active case • Mycobacteriology laboratory personnel • Immigrants from high-burden countries • Residents and employees of high-risk congregate settings	Low: • No risk factors Intermediate: • Diabetes • Chronic renal failure • Intravenous drug use High: • Children < 5 years • HIV infection • Immunosuppressive therapy • Abnormal chest x-ray consistent with prior TB • Silicosis

* For children under 5 years of age use TST rather than an IGRA in all situations

D. Therapy
   1. Treatment of latent TB infection
      a. The goal is to prevent latent (asymptomatic) infection from progressing to clinical disease.
      b. Treatment of latent TB infection is recommended for the following people:
         i. HIV infected persons
         ii. Close contacts of people with a diagnosed infectious TB
         iii. People with abnormal chest radiographs that show fibrotic lesions, likely to represent old, healed TB
         iv. Immunosuppressed persons (e.g., organ transplant recipients, taking the equivalent of 15 mg/day or more of prednisone for 1 month or longer, receiving TNF-alpha antagonists)
         v. Foreign-born people from high-prevalence countries (immigration within 5 years)
         vi. Persons who inject drugs
         vii. People working at or living in high-risk congregate settings (e.g., correctional facilities, nursing homes, homeless shelters, hospital, and other health care facilities)
         viii. Mycobacteriology laboratory personnel
         ix. Children under 4 years of age, or children and adolescents exposed to adults in high-risk categories
      c. Dosing regimens
         i. Patients who are not infected with HIV
            (a) Rifapentine 900 mg plus isoniazid 900 mg weekly for 12 weeks (as directly observed therapy or self-administered therapy)
            (b) Rifampin 600 mg daily for 4 months

(c) Rifampin 600 mg daily plus isoniazid 300 mg daily for 3 months
(d) Isoniazid 300 mg daily or 900 mg twice weekly for 6–9 months (9 months preferred, especially for children; directly observed therapy recommended for twice weekly regimen)

ii. Patients who are coinfected with HIV
(a) Rifapentine 900 mg orally plus isoniazid 15 mg/kg orally (900 mg maximum) plus pyridoxine 50 mg orally, all once weekly for 12 weeks
(b) Isoniazid 300 mg orally plus rifampin 600 mg orally plus pyridoxine 25–50 mg orally, all daily for 3 months (watch for drug interactions with rifampin)
(c) Alternatives: isoniazid 300 mg orally plus pyridoxine 25–50 mg orally daily for 6-9 months (especially if rifamycin drug interactions are a concern); rifampin 600 mg orally daily for 4 months; isoniazid 300 mg orally plus rifapentine orally plus pyridoxine 25–50 mg orally, all daily for 4 weeks

iii. Areas with multidrug-resistant isolates: Two drugs with activity against the isolate for 6–12 months

Patient Case

9. R.J. is a 32-year-old HIV-positive man who presents to the clinic with increased weight loss, night sweats, and a cough productive of sputum. He is currently receiving darunavir/ritonavir 800 mg/100 mg daily, tenofovir disoproxil fumarate 300 mg daily, emtricitabine 200 mg daily, fluconazole 200 mg/day orally, and trimethoprim/sulfamethoxazole double strength daily. A sputum sample is positive for acid-fast bacillus. R.J. lives in an area with a low incidence of multidrug-resistant TB. Which is the best initial treatment?

A. Initiate isoniazid, rifampin, and pyrazinamide with no change in HIV medications.
B. Initiate isoniazid, rifampin, and pyrazinamide; increase the dosage of darunavir/ritonavir; and use a higher dosage of rifampin.
C. Initiate isoniazid, rifabutin, pyrazinamide, and ethambutol, with a lower dosage of rifabutin.
D. Initiate isoniazid, rifabutin, pyrazinamide, and ethambutol, and decrease the dosage of darunavir/ritonavir.

2. Treatment of active TB infection (Tables 10 and 11)
a. Principles of treatment
i. Regimens must contain many drugs to which the organisms are susceptible.
ii. Drug therapy must continue for a sufficient period.

Table 10. Pharmacotherapeutic Agents in the Treatment of Tuberculosis

First-Line Agents	Second-Line Agents
Isoniazid	Amikacin/kanamycin
Rifampin	Bedaquiline
Pyrazinamide	Capreomycin
Ethambutol	Cycloserine
	Ethionamide
	Fluoroquinolones
	Linezolid
	Para-aminosalicylic acid
	Pretomanid
	Rifabutin
	Rifapentine
	Streptomycin

b. Therapeutic options for treating active TB (Note: Any regimen administered two, three, or five times/week should be done by directly observed therapy.)

Table 11. Treatment of Tuberculosis

	Patients without HIV		Patients with HIV	
Recommended	**Antibiotic**	**Regimen**	**Antibiotic**	**Regimen**
Intensive Phase[a]	Isoniazid[b] Rifampin Pyrazinamide Ethambutol	Treat for 2 months (daily or five times weekly)	Isoniazid Rifampin or rifabutin Pyrazinamide Ethambutol	Treat for 2 months (daily)
Continuation Phase	Isoniazid Rifampin	Treat for 4 months[c] (daily or five times weekly)	Isoniazid Rifampin or rifabutin	Treat for 4 months[d] (daily)
Optional (less efficacy)[e]	**Antibiotic**	**Regimen**	**Antibiotic**	**Regimen**
Intensive Phase[a]	Isoniazid Rifampin Pyrazinamide Ethambutol	Treat for 2 months (three times weekly or daily for two weeks followed by two times weekly)	N/A	N/A
Continuation Phase	Isoniazid Rifampin	Treat for 4 months (three times weekly)	N/A	N/A

[a]If TB isolate is susceptible to both INH and RIF, then ethambutol can be dropped from the intensive phase.

[b]Pyridoxine should be given to all those receiving isoniazid and at increased risk of neuropathy (e.g., pregnant women, breastfeeding infants, HIV infected persons, patients with diabetes, alcoholism, malnutrition, or chronic renal failure, persons of advanced age).

[c]Extend to 7 months if cavitary lesions on chest x-ray and positive sputum culture after intensive phase.

[d]Extend to 7 months if patient not receiving ART.

[e]Efficacy diminishes as the number of weekly doses decreases.

c. Concurrent therapy in patients with HIV
   i. For ART-naive patients, ART should be initiated within 2 weeks when the CD4 count is less than 50 cells/mm^3 and by 8 weeks for all others.
   ii. PIs and NNRTIs (except for efavirenz or nevirapine) should not be administered concurrently with rifampin; INSTIs can be administered with rifampin (except elvitegravir, bictegravir, and cabotegravir), but doses need to be adjusted; NRTIs can be administered with rifampin, except for tenofovir alafenamide.
   iii. A washout period of 1–2 weeks may be necessary once rifampin is discontinued before PIs, elvitegravir, or NNRTIs are initiated.
   iv. Rifabutin can be substituted for rifampin; patients may take NRTIs and NNRTIs with rifabutin except for tenofovir alafenamide, but rifabutin doses may need to be increased to 450–600 mg daily (see HIV guidelines).
   v. Patients may take PIs with rifabutin unless the PI is boosted with cobicistat; if the PI is boosted with ritonavir, the rifabutin dose should be decreased to 150 mg every day.
   vi. Elvitegravir and bictegravir should not be used with rifabutin.
   vii. Patients taking rifabutin and PIs, INSTIs, or NNRTIs should have HIV RNA and rifabutin concentrations performed periodically.
   viii. Rifapentine should only be given to virally suppressed patients receiving an efavirenz-, dolutegravir- or raltegravir-based regimen.

d. Known drug resistance to isoniazid: Administer rifampin, pyrazinamide, ethambutol, and moxifloxacin or levofloxacin for 2 months; rifabutin may be substituted for rifampin in patients with HIV. Continuation phase should be completed with rifampin (or rifabutin) plus ethambutol plus moxifloxacin (or levofloxacin) for 4 additional months.
e. Total duration of therapy should be based on number of doses received, not on calendar time.
    i. Pulmonary TB: 6 months
    ii. Pulmonary TB and culture positive after 2 months of TB treatment: 9 months
    iii. Extrapulmonary TB with central nervous system (CNS) infection: 9–12 months
    iv. Extrapulmonary TB with bone or joint involvement: 6–9 months
    v. Extrapulmonary TB in other sites: at least 6 months

Patient Cases

10. Which represents the best follow-up for R.J. (from Patient Case 9)?
    A. Treatment with the initial drugs should continue for 6 months.
    B. Treatment can be decreased to isoniazid and a rifamycin after 2 months for a total treatment of 18–24 months.
    C. Treatment can be decreased to isoniazid and a rifamycin after 2 months for a total treatment of 6 months; HIV RNA concentrations should be observed closely during therapy.
    D. Treatment can be decreased to isoniazid, a rifamycin, and either pyrazinamide or ethambutol after 2 months for a total treatment of 6 months; HIV RNA concentrations should be observed closely during therapy.

11. L.F. is a 55-year-old man (73 kg) who was involved in a motor vehicle accident with subsequent rib fractures and bilateral pneumothoraces. He is admitted to the ICU and mechanically ventilated. He is started on levofloxacin which after 3 days is switched to piperacillin/tazobactam and vancomycin. After 5 days of broad spectrum antibiotics his temperature continues to spike. A blood culture is positive for *Candida krusei*. What is the best treatment for L.F.?
    A. Fluconazole 400 mg IV daily for 7 days following the first negative blood culture.
    B. Micafungin 100 mg IV daily for 14 days following the first negative blood culture.
    C. Amphotericin B lipid formulation 3 mg/kg/day for 14 days following the first negative blood culture.
    D. Voriconazole 200 mg IV twice daily for 7 days following the first negative blood culture.

IV. FUNGAL PHARMACOTHERAPY

A. Candida
    1. Background
        a. *C. albicans*, *C. krusei*, *C. parapsilosis*, *C. tropicalis*, *C. glabrata*, *C. auris*
        b. Risk factors:
            i. Broad spectrum antibiotics
            ii. Central catheters, urinary catheters, etc. (remove if found to be the source of infection)
            iii. Prosthetic devices
            iv. Immunocompromised (chemotherapy, radiation, corticosteroid, HIV, etc.)
    2. Therapy
        a. Oral/esophageal candidiasis (see II. Opportunistic Infections: Patients With HIV, D. Candida Infections)

b. Candidemia
    i. Echinocandin (caspofungin, anidulafungin, rezafungin, or micafungin)
    ii. Fluconazole: only use if known or suspected fluconazole-sensitive organism (400 mg/day or weight-based dosing 6 mg/kg/day)
    iii. Amphotericin B lipid formulation – for resistance or intolerance to other antifungals
    iv. Treat for 14 days after first negative blood culture
c. Endocarditis
    i. Amphotericin B lipid formulation ± flucytosine or high dose echinocandin
    ii. Fluconazole (or voriconazole or posaconazole) can be used as step down therapy for sensitive isolates
    iii. Replace the valve and treat for 6 weeks
    iv. Consider chronic suppressive therapy with fluconazole for patients unable to undergo cardiac surgery
d. Osteomyelitis/Septic arthritis
    i. Fluconazole for 6-12 months
    ii. Echinocandin for 2 weeks followed by fluconazole for 6-12 months
    iii. Amphotericin B lipid formulation for 2 weeks followed by fluconazole for 6-12 months
    iv. Same recommendations for septic arthritis except total therapy is only 6 weeks
e. Urinary tract infections
    i. Remove indwelling catheters, nephrostomy tubes, stents, etc.
    ii. Asymptomatic: treat only if patient is neutropenic or undergoing urologic manipulation associated with mucosal trauma or bleeding
    iii. Symptomatic
        (a) Fluconazole for 2 weeks
        (b) Amphotericin B deoxycholate (not liposomal preparations) (1-7 days) or flucytosine (7-10 days) for fluconazole resistant organisms
        (c) Other azoles and echinocandins do not achieve adequate urinary concentrations
f. Invasive Candidiasis in the Intensive Care Unit
    i. Empiric treatment
        (a) Use for patients with unexplained fever and risk factors: *Candida* colonization, severe illness, broad spectrum antibiotics, recent abdominal surgery, necrotizing pancreatitis, dialysis, total parenteral nutrition, corticosteroids, central venous catheter
        (b) Echinocandin therapy recommended
        (c) Fluconazole use only in patients without recent azole use or colonization with azole-resistant organisms
        (d) Amphotericin B lipid formulation if patient intolerant to other antifungals
        (e) Duration: 2 weeks if patient responds or 4-5 days with no response
    ii. Prophylaxis
        (a) Fluconazole 400 mg daily in ICUs where invasive candidiasis occurs in more than 5% of patients
        (b) Echinocandins can be used alternatively

B. Histoplasmosis
1. Background
    a. *Histoplasma capsulatum*
    b. Endemic regions: lower Mississippi and Ohio valleys
    c. Organisms in excrement are aerosolized and inhaled
    d. Signs and symptoms: lymphadenopathy, splenomegaly, fever, weight loss, headache, chills, cough, chest pain, myalgias, fatigue

2. Therapy
    a. 50% mortality even with therapy – relapses are frequent
    b. Moderate to severe illness: Lipid formulation amphotericin B (3–5 mg/kg/day) for at least 1-2 weeks followed by itraconazole to complete 12 weeks of therapy
    c. Mild illness: itraconazole 200 mg three times daily for 3 days and then twice daily for 12 weeks (may need to extend to 12-24 months in patients with chronic or disseminated disease)

C. Coccidioidomycosis
1. Background
    a. *Coccidioides immitis*
    b. Endemic regions: California, Arizona, Nevada, New Mexico, Utah, Texas
    c. Organisms in soil are aerosolized and inhaled
    d. Signs and symptoms: cough, sputum production, chest pain, malaise, fever, chills, night sweats, anorexia, weakness, arthralgias
2. Therapy
    a. Consider not treating in immunocompetent host
    b. Fluconazole 400 mg daily (5 mg/kg/day with use of higher doses optional in patients with meningitis and/or bone/joint infections) or itraconazole 200 mg twice daily for 3–6 months
    c. Severe/diffuse/disseminated disease: amphotericin B lipid formulation (3–5 mg/kg/day) until improvement then fluconazole or itraconazole for at least a year

D. Blastomycosis
1. Background
    a. *Blastomyces dermatitidis*
    b. Endemic regions: Southeastern states, Ohio and Mississippi river basins, and Great Lakes region including the St. Lawrence seaway
    c. Sources: soil – organisms in soil are aerosolized and inhaled
    d. Signs and symptoms: cough, sputum production, chest pain, malaise, fever, chills, weakness, arthralgias
    e. Cutaneous manifestations (occurs in 40-80% of patients): small papulopustular lesions that spread to form a crusted, heaped-up lesion or an ulcerative pustular lesion
2. Therapy
    a. Itraconazole 200 mg three times daily for 3 days and then twice daily for 24 weeks
    b. Severe/life threatening disease: amphotericin B lipid formulation (3–5 mg/kg/day) until improvement then itraconazole for 6-12 months

E. Aspergillosis
1. Background
    a. *Aspergillus fumigatus*
    b. Ubiquitous in the environment
    c. Sources: grows in stored hay/grain, decaying vegetation, soil, compost piles, and manure – common during hospital renovation / construction, in potted plants, and air conditioner filters – organisms are aerosolized and inhaled
    d. Allergic bronchopulmonary aspergillosis – in asthma patients, aspergillosis causes hypersensitivity reaction and granuloma formation (treat with prednisone)
    e. Pneumonia – secondary to prolonged neutropenia; high fever and dense pulmonary infiltrates – rapidly progressing and universally fatal in bone marrow transplant patients

2. Therapy
    a. Voriconazole 6 mg/kg intravenously twice daily for two doses and then 4 mg/kg intravenously twice daily or 200-300 mg orally twice daily (oral is preferred because of cyclodextrin solvent in intravenous solution)
    b. Alternatives: isavuconazole 200 mg every 8 hours for six doses and then 200 mg daily or amphotericin B lipid formulation (3-5 mg/kg/day)
    c. Echinocandins only if azoles and amphotericin are contraindicated
    d. Treat for 6-12 weeks
3. Prophylaxis
    a. Recommended for at-risk patients with prolonged neutropenia, graft-versus-host disease or lung transplant
    b. Agent is dependent upon type of transplant and individual transplant centers, but can include voriconazole, itraconazole, posaconazole, isavuconazole, or inhaled amphotericin

F. Mucormycosis
1. Background
    a. *Rhizopus* spp. and *Mucor* spp.
    b. Ubiquitous in the environment
    c. Sources: decaying organic matter – organisms are aerosolized and inhaled
    d. Signs and symptoms: fever, cough, shortness of breath (pulmonary); can also cause sinusitis with associated symptoms or cutaneous infections
2. Therapy
    a. Must be multimodal
        i. Reversal or discontinuation of underlying predisposing factors (if possible)
        ii. Early administration of active antifungal agents
        iii. Complete removal of all infected tissues
        iv. Use of various adjunctive therapies
    b. Amphotericin B lipid formulation (5–10 mg/kg/day) with or without posaconazole or isavuconazole until improvement then isavuconazole or posaconazole monotherapy
    c. Treat until resolution of infection (usually months)

Patient Case

12. A.B. is a 55-year-old woman who presents to your clinic with toenail discoloration with a few of her toenails separating from the nail bed. She is diagnosed with onychomycosis. What is the best treatment for A.B.?
    A. Fluconazole 200 mg orally daily for 14 days.
    B. Itraconazole 200 mg orally daily for 28 days.
    C. Miconazole cream applied twice daily to toenails for 2 months.
    D. Terbinafine 250 mg orally daily for 3 months.

G. Superficial fungal infections
1. Background
    a. Caused by dermatophytes (*Microsporum*, *Trichophyton*, *Epidermophyton*)
    b. More common in males than females
    c. More common in tropical, humid climates
    d. Transmitted person to person, via soil contact and via animal contact

2. Tinea capitis – infection of the scalp
    a. Peak incidence of 3-9 years of age, more common in nonwhites
    b. Spores invade the hair shaft leading to hair loss without inflammation or spores spread beyond the hair shaft leading to inflammation
    c. Therapy:
        i. Griseofulvin (preferable for *Microsporum*) 10–15 mg/kg/day for 4–12 weeks
        ii. Terbinafine (preferable for *Trichophyton*): Weight less than less than 20 kg: 62.5 mg; 20–40 kg: 125 mg; greater than 40 kg: 250 mg daily for 4 weeks
        iii. Itraconazole, fluconazole – alternatives; treat for 4–6 weeks
        iv. Selenium sulfide 2.5% shampoo (reduces spread of infection and reinfection)
3. Tinea pedis – infection of the foot
    a. Increase in frequency with age; more common in men than women, and in those who wear shoes
    b. Moccasin-like distribution (difficult to treat) or intertrigenous involvement which may lead to secondary bacterial infection
    c. Therapy:
        i. Topical antifungal agent twice daily until clear
        ii. Terbinafine, itraconazole, or fluconazole for severe or resistant cases
4. Tinea cruris – infection of the groin and thigh
    a. More common in males than females
    b. Predisposing factors include obesity, tight-fitting clothes, wet swimsuits, etc.
    c. Therapy:
        i. Topical antifungals twice daily for 3-4 weeks
        ii. Loose-fitting cotton underwear and good hygiene
5. Tinea corporis – "ringworm"
    a. Common in hot, humid climates – transmitted person to person
    b. Asymptomatic or pruritic annular plaque – scaling, crusting, vesicle formation and papules on nonhairy skin
    c. Therapy:
        i. Topical antifungal twice daily for 2-4 weeks
        ii. Terbinafine or itraconazole for extensive skin involvement
6. Onychomycosis – nail infection
    a. Increases with age – affects 5% of the population
    b. Predisposing factors include superficial fungal infection of feet or hands, repeated minor trauma with heat and moisture
    c. Nail discoloration, subungual hyperkeratosis, separation of nail from bed
    d. Therapy:
        i. Terbinafine
        ii. Itraconazole (pulse or continuous therapy)
        iii. Onychomycosis specific topical agents: efinaconazole, tavaborole, or ciclopirox
        iv. Duration: fingernails: 6 weeks; toenails: 12 weeks (longer if using topical agents)

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: D
The patient should be treated at this time; a potent combination ART should be initiated in all HIV-infected patients, regardless of CD4 count (Answer A is incorrect). Combination therapy of tenofovir, emtricitabine, and dolutegravir is a recommended initial therapeutic regimen (Answer D is correct). Regimens without an NNRTI, PI, or INSTI are not indicated for HIV (Answer B is incorrect). The regimen of abacavir, lamivudine, and atazanavir/ritonavir is not a recommended or alternative option. It should only be used if recommended or alternative options are not appropriate (Answer C is incorrect).

2. Answer: B
A patient taking abacavir should be screened for the presence of the *HLA-B*5701* allele before initiating therapy. If the patient is positive for this allele, the risk of hypersensitivity reactions is increased (Answer B is correct). Although abacavir may increase AST and ALT concentrations, the incidence of hepatotoxicity is extremely low in patients without the *HLA-B*5701* allele and these labs do not need to be checked before starting therapy. (Answer A is incorrect). Endocrine disturbances (e.g., hyperglycemia, fat redistribution, lipid abnormalities) are more associated with PIs (Answer C is incorrect). Abacavir does not cause hyperbilirubinemia; therefore, the patient need not be monitored for this (Answer D is incorrect).

3. Answer: A
When the CD4 count decreases to 135 cells/mm^3, the patient should receive primary prophylactic treatment against PJP (CD4 count less than 200 cells/mm^3) (Answer A is correct). Primary prophylaxis is necessary for MAC when the CD4 count is less than 50 cells/mm^3 (Answer D is incorrect). For CMV, patients with CD4 counts less than 50 cells/mm^3 should receive regular funduscopic examinations (Answer C is incorrect). In general, primary prophylaxis is not used for cryptococcal meningitis (Answer B is incorrect).

4. Answer: C
Although pentamidine would be an appropriate alternative therapeutic option for a patient who is HIV positive with PJP, the optimal empiric therapy is trimethoprim/sulfamethoxazole intravenously with adjuvant prednisone therapy for 21 days (Answer A is incorrect and answer C is correct). The regimen may be changed to trimethoprim/sulfamethoxazole orally after the patient has clinical improvement. Although trimethoprim/sulfamethoxazole is the drug of choice for PJP, adjuvant prednisone therapy is indicated because the patient's A-a gradient is 55, and his PO_2 is less than 70 mm Hg (Answer B is incorrect). Atovaquone is indicated only for patients with mild to moderate PJP who cannot tolerate trimethoprim/sulfamethoxazole. This patient does not meet this criterion (Answer D is incorrect).

5. Answer: B
Patients with cryptococcal meningitis should ideally be treated with liposomal amphotericin and flucytosine for at least 2 weeks, followed by fluconazole for at least 8 weeks (Answer B is correct). Although amphotericin B deoxycholate with fluconazole is an alternative, this is not the best option (Answer A is incorrect). Fluconazole alone is also an alternative but should only be used when none of the amphotericin products is an option for therapy (Answer C is incorrect). Because of the higher mortality when ART is begun early in cryptococcal meningitis therapy, initiation of ART should be delayed until 4–6 weeks after beginning appropriate antifungal therapy (Answer D is incorrect).

6. Answer: B
Maintenance therapy for cryptococcal meningitis with fluconazole can be discontinued after a minimum of 1 year of long-term maintenance therapy if the CD4 count increases to more than 100 cells/mm^3 for 3 months or longer after potent combination ART (Answer B is correct and answer D is incorrect). Because this patient's CD4 counts have been greater than 100 cells/mm^3 for at least 3 months, maintenance therapy can be discontinued after he has been treated for 1 year (Answers A and C are incorrect).

7. Answer: B
For the treatment of MAC, azithromycin plus ethambutol for at least 12 months is the best therapeutic combination; this combination includes one of the newer macrolides and a second agent (ethambutol is usually the preferred second agent) (Answer B is correct). Therapy may be discontinued after 12 months if CD4 counts increase with potent combination ART and if the patient

is asymptomatic. Clarithromycin plus ethambutol for 2 weeks, followed by maintenance with clarithromycin alone, is incorrect because there is no induction period for MAC (Answer A is incorrect). A therapeutic regimen of clarithromycin plus isoniazid is inappropriate because isoniazid has no activity against MAC (Answer C is incorrect). Although ethambutol plus rifabutin has activity against MAC, current guidelines recommend regimens include either azithromycin or clarithromycin; therefore, the ethambutol plus rifabutin regimen is not the treatment of choice (Answer D is incorrect).

8. Answer: D

A patient with an induration greater than 15 mm after a TST for TB needs to be assessed for treatment. Because this patient works at a high-risk congregate setting (i.e., the long-term care facility), he needs to be treated for latent TB (Answer A is incorrect). The booster effect is a phenomenon associated with an initial small reaction causing immunologic stimulation, followed by a larger reaction with a subsequent test. This patient had an initial large reaction (18-mm induration) (Answer B is incorrect). Age is not a factor to consider in treating latent TB (Answer C is incorrect). Initiating rifampin plus isoniazid for a short 3-month course is the best recommendation for managing this patient's positive TST (Answer D is correct).

9. Answer: C

Rifampin should not be administered concurrently with protease inhibitors (rifampin will induce the metabolism of darunavir and ritonavir) (Answer A is incorrect). Patients who are HIV positive should be initiated on four drugs for TB, and darunavir should not be used with rifampin, even at a higher dose (Answer B is incorrect). The best recommendation is isoniazid, rifabutin, pyrazinamide, and ethambutol, with a lower dose of rifabutin; it includes the four drugs for TB and a lower dose of rifabutin (because of darunavir/ritonavir inhibition) (Answer C is correct). The darunavir/ritonavir dose does not need to be changed when rifabutin is added (Answer D is incorrect).

10. Answer: C

For this patient, only the rifamycin and isoniazid need to be continued after 2 months of therapy with the four drugs for TB (Answer A is incorrect). The regimen can be simplified to a rifamycin and isoniazid after 2 months, but the recommended total treatment duration is 6 months (Answers B and D are incorrect). The concentrations of HIV RNA should be monitored closely because of potential alterations in drug concentrations of the PI (Answer C is correct).

11. Answer: B

Candida krusei is an organism that is frequently resistant to azole antifungals, including fluconazole; therefore, this agent should not be used in this situation (Answer A is incorrect). Voriconazole would need to be used longer than 7 days and in conjunction with an echinocandin or amphotericin against *C. krusei* (Answer D is incorrect). The best choice would be either an echincocandin or amphotericin product (although the newer azoles, posaconazole and isavuconazole, do have some activity against *C. krusei*). Given its lower side effect profile and lack of adjustments needed for renal or hepatic dysfunction, micafungin is the best choice in this situation (Answer B is correct). The length of therapy is also correct, treatment for 14 days after the first negative blood culture. Although an amphotericin B lipid formulation would be a second-line option, the higher incidence of side effects associated with its use make it not the best choice (Answer C is incorrect).

12. Answer: D

Onychomycosis needs to be treated for a long period of time, generally 3 months. Although fluconazole is active against the organisms that cause onychomycosis and systemic therapy is generally best, a 14-day course would not be long enough to effectively treat the infection (Answer A is incorrect). Itraconazole is one of the drugs of choice for onychomycosis, in either a continuous or pulse therapeutic regimen. However, once again, 28 days is not long enough for treatment (Answer B is incorrect). There are a number of different topical antifungal medications that can be used for onychomycosis. However, miconazole cream is not one of them. Also, topical treatment requires longer therapy than systemic treatment (Answer C is incorrect). Terbinafine is one of the drugs of choice for onychomycosis and the treatment duration, 3 months, is correct (Answer D is correct).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: D

Transmission of HIV to a child is decreased if the mother's viral load is decreased. The benefits of therapy far outweigh the risk (Answer A is incorrect). A potent combination ART regimen given throughout the pregnancy is the most appropriate therapeutic regimen for an asymptomatic patient with HIV who is pregnant (even in the first trimester) and has a low CD4 count and high viral load (Answer D is correct). Although zidovudine 300 mg twice daily orally throughout the pregnancy, followed by zidovudine during labor and to the child for 6 weeks, was the regimen originally studied to decrease HIV transmission, potent combination ART is indicated because of the patient's low CD4 count and high viral load; therefore, single-drug therapy is inappropriate (Answer B is incorrect). A single dose of nevirapine at the onset of labor will not affect viral load or lower the risk of HIV transmission as much as potent combination ART throughout the pregnancy (Answer C is incorrect).

2. Answer: A

The patient should be told that dolutegravir can cause insomnia (Answer A is correct). This patient should be told to talk to a pharmacist about the current combination therapy because there are many drug interactions with antiretroviral agents. However, neither dolutegravir nor tenofovir inhibit CYP3A4 (Answer C is incorrect). Informing the patient to cut the dose in half if there are adverse effects is incorrect because antiretroviral drugs should never be used below the recommended dose (Answer B is incorrect). Informing the patient that tenofovir and emtricitabine cause additive peripheral neuropathy is incorrect because neither of these drugs is associated with that adverse effect (Answer D is incorrect).

3. Answer: B

Patients with cryptococcal meningitis should always receive maintenance therapy (Answer A is incorrect). One of the principles of treating AIDS-related illnesses is that the infections are seldom curable, and generally long-term secondary prevention is required. Weekly amphotericin B has been studied for secondary prophylaxis, but fluconazole is the better agent because of its ease of administration and lower toxicity (Answer B is correct and answer C is incorrect). The agents that are effective for PJP prophylaxis have no activity against *Cryptococcus (*Answer D is incorrect).

4. Answer: C

The number of patients needed to treat with isoniazid over rifampin to prevent one progression to active disease is $200 = 1/(0.008 - 0.003)$ (Answers A, B, and D are incorrect and answer C is correct).

5. Answer: D

Pyrimethamine plus clindamycin and leucovorin for 6 weeks is the correct choice for treating toxoplasmosis in a patient who is HIV positive, not taking antiretrovirals, and taking dapsone for PJP prophylaxis (Answer D is correct). Atovaquone is not a preferred therapy, although data support its effectiveness in combination with sulfadiazine or pyrimethamine (Answer A is incorrect); trimethoprim/sulfamethoxazole is not a preferred agent for treatment or secondary prophylaxis given its lower in vitro activity when compared to pyrimethamine/sulfadiazine; it may be used as an alternative if pyrimethamine is not available (Answer B is incorrect). Pyrimethamine and sulfadiazine are the first-line agents for toxoplasmosis; however, leucovorin should always be used with pyrimethamine to prevent myelosuppression (Answer C is incorrect).

6. Answer: D

Fluconazole has no activity against aspergillus, so it would not be an option for therapy (Answer A is incorrect). Although voriconazole has activity against aspergillus, there is a significant interaction with rifampin, resulting in lower voriconazole concentrations (Answer B is incorrect). Isavuconazonium does have activity against aspergillus, but levels are significantly decreased in a patient receiving rifampin (Answer C is incorrect). Amphotericin lipid formulation would be the best option because of its activity against aspergillus and lack of drug interaction with any of the TB medications (Answer D is correct).

7. Answer: B

Because the patient is symptomatic and her sputum is acid-fast bacillus positive, she should be treated for an active TB infection. The recommended therapy for active TB is isoniazid, rifampin, pyrazinamide, and ethambutol for 2 months, followed by isoniazid and

rifampin for 4 more months (Answer B is correct). Patients should be initiated on at least three antibiotics for the first 2 months (Answers A and C are incorrect). Although fluoroquinolones have some activity against TB, their use as first-line monotherapy is inappropriate (Answer D is incorrect).

8. Answer: C

Data are continuous and probably normally distributed (given the large population of 350 patients in the study); therefore, a parametric test is indicated. The t-test is the best parametric test for comparing two groups (Answer C is correct). Although an analysis of variance is a parametric test, it is used to compare more than two groups (Answer A is incorrect). A chi-square test is used to compare nominal or categorical data between two groups (Answer B is incorrect). The end points in this study are continuous and should therefore not be compared using this statistical test. The Wilcoxon rank sum test is a nonparametric analog to the t-test (Answer D is incorrect).

9. Answer: A

Valganciclovir therapy should be continued in an HIV-positive patient with CMV retinitis until the patient's CD4 count is above 100 cells/mm^3 for at least 3 months (Answer A is correct, answers B, C and D are incorrect). There is no minimum duration of therapy for CMV retinitis, as there is with MAC or cryptococcal infections. Therapy would need to be reinitiated if his CD4 count fell back below 100 cells/mm^3. In patients with CMV retinitis, all lesions must be inactive and the decision to stop maintenance treatment made in collaboration with an ophthalmologist.

10. Answer: C

Until the Candida can be proven to be fluconazole susceptible, an echinocandin is first-line therapy (Answer C is correct; Answer B is incorrect). Liposomal amphotericin B should only be used when other therapies are not tolerated (Answer A is incorrect). Olorofim is only FDA approved as an inhaled formulation, which is inadequate to treat Candidemia (Answer D is incorrect).

11. Answer: C

Because the patient has a sulfonamide allergy, trimethoprim/sulfamethoxazole is not an option, even though the dose is correct (Answer A is incorrect). All of the other agents are potential options. However, the dapsone dose is incorrect, and dapsone should be used with caution in patients with sulfonamide allergies. When used alone it must be dosed daily (Answer B is incorrect). Moreover, pentamidine is difficult to administer because it must be done by nebulization (Answer D is incorrect). Therefore, the best choice is atovaquone (Answer C is correct).

12. Answer: A

Given the fact that this patient is hospitalized and his infection is worsening, this can be considered a moderate to severe case of Histoplasmosis. The correct regimen is 1-2 weeks of an amphotericin B lipid formulation followed by itraconazole to complete a 12-week course (Answer A is correct). The echinocandins appear to be ineffective against Histoplasma so micafungin should not be used (answer B is incorrect). Although both voriconazole and isavuconazole have activity against Histoplasma they currently aren't recommended based on limited to no clinical data supporting their use. Voriconazole also has significant drug interactions (as does itraconazole) and isavuconazole is expensive (answers C and D are incorrect).

13. Answer: B

This patient has active tuberculosis as demonstrated by his symptoms, positive sputum, and positive IGRA test. Patients with active tuberculosis should be treated with 4 drugs (rifampin, isoniazid, pyrazinamide, ethambutol) for 2 months and 2 drugs (rifampin and isoniazid) for 4 months (answers C and D are incorrect). Although a regimen administered 2 and 3 times weekly is optional, it is not the recommended therapy (answer A is incorrect). However, in this man experiencing homelessness, it may be necessary if he cannot adhere to daily or five-times-weekly dosing. Ideally, active tuberculosis treatment should be given either daily or 5 times weekly (Answer B is correct).

Critical Care

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Learning Objectives

1. Interpret hemodynamic parameters and acid-base status in critically ill patients.
2. Employ the appropriate use of fluids, vasopressors, antibiotics, and corticosteroids in patients with sepsis or septic shock.
3. Recommend strategies to optimize care for targeted temperature management after cardiac arrest and for acute intracranial hemorrhage.
4. Manage therapeutic options to minimize delirium and provide optimal analgesia, sedation, neuromuscular blockade, and nutritional support in critically ill patients.
5. Select therapeutic options to prevent stress ulcers, venous thromboembolism, hyperglycemia, and ventilator-associated pneumonia in critically ill patients.

Abbreviations in This Chapter

ABG	Arterial blood gas
AG	Anion gap
AHA	American Heart Association
ARDS	Acute respiratory distress syndrome
BMI	Body mass index
BPS	Behavioral Pain Scale
BSA	Body surface area
BUN	Blood urea nitrogen
CAM-ICU	Confusion Assessment Method for the ICU
CI	Cardiac index
CPOT	Critical-Care Pain Observation Tool
CPR	Cardiopulmonary resuscitation
CVP	Central venous pressure
D_5W	5% Dextrose
DBP	Diastolic blood pressure
EN	Enteral nutrition
EPS	Extrapyramidal symptoms
FiO_2	Fraction of inspired oxygen
GI	Gastrointestinal
H_2	Histamine-2
HIT	Heparin-induced thrombocytopenia
ICDSC	Intensive Care Delirium Screening Checklist
ICH	Intracranial hemorrhage
ICU	Intensive care unit
INR	International normalized ratio
IPH	Intraparenchymal hemorrhage
LMWH	Low-molecular-weight heparin
MAP	Mean arterial pressure
OGT	Orogastric feeding tube
$Paco_2$	Partial pressure of carbon dioxide
PAOP	Pulmonary artery occlusion pressure
PCWP	Pulmonary capillary wedge pressure
PN	Parenteral nutrition
PPI	Proton pump inhibitor
PPV	Pulse pressure variation
RASS	Richmond Agitation-Sedation Scale
RQ	Respiratory quotient
SAH	Subarachnoid hemorrhage
SAS	Sedation-Agitation Scale
SBP	Systolic blood pressure
SSC	Surviving Sepsis Campaign
SUP	Stress ulcer prophylaxis
SVR	Systemic vascular resistance
SVV	Stroke volume variation
TOF	Train-of-four
VTE	Venous thromboembolism
WBC	White blood cell count

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

1. A 58-year-old woman remains intubated in the intensive care unit (ICU) after a recent abdominal operation. In the operating room, she receives more than 10 L of fluid and blood products, but has received aggressive diuresis with furosemide postoperatively. In the past 3 days, she has generated 12 L of urine output, and her blood urea nitrogen (BUN) and serum creatinine (SCr) have steadily increased to 40 and 1.5 mg/dL, respectively. Her urine chloride (Cl) concentration was 9 mEq/L (24 hours after her last dose of furosemide). This morning, her arterial blood gas (ABG) reveals pH 7.50, $Paco_2$ 46 mm Hg, and bicarbonate (HCO_3^-) 34 mEq/L. Her vital signs include blood pressure 85/40 mm Hg and heart rate 110 beats/minute. Which action is best to improve her acid-base status?
   A. 0.9% sodium chloride bolus.
   B. 5% dextrose (D_5W) bolus.
   C. Hydrochloric acid infusion.
   D. Acetazolamide intravenously.

2. A 21-year-old man (weight 80 kg) admitted 1 day ago after a gunshot wound to the abdomen is receiving mechanical ventilation and is thrashing around in bed and pulling at his endotracheal tube. His score is +3 on the Richmond Agitation-Sedation Scale (RASS). The patient is negative for delirium according to the Confusion Assessment Method for the ICU (CAM-ICU). His pulmonary status precludes extubation, and the attending physician estimates that he will remain intubated for at least 48 more hours. The medical team has decided that his RASS goal should be between 0 and -1. He is receiving a fentanyl infusion (150 mcg/hour), which has been adequately controlling his pain (Critical-Care Pain Observation Tool [CPOT] less than 3 for 24 hours). Vital signs include blood pressure 110/70 mm Hg and heart rate 110 beats/minute. His baseline QTc interval is 460 milliseconds. Which is the best intervention for achieving this patient's RASS goal?
   A. Initiate a dexmedetomidine 1-mcg/kg loading dose over 10 minutes, followed by 0.7 mcg/kg/hour.
   B. Initiate a lorazepam 3-mg intravenous load, followed by a lorazepam 3-mg/hour infusion.
   C. Initiate propofol at 5 mcg/kg/minute and titrate by 5 mcg/kg/minute every 5 minutes as needed.
   D. Initiate haloperidol 1 mg intravenously, and double the dose every 1 hour as needed.

3. A 62-year-old woman is admitted to the medical ICU for respiratory dysfunction necessitating mechanical ventilation. She has no significant medical history. Her chest radiograph reveals bilateral lower lobe infiltrates, her white blood cell count (WBC) is 21×10^3 cells/mm^3, lactate is 1.7 mmol/L, temperature is 103.3°F (39.6°C), blood pressure is 82/45 mm Hg (normal for her is 115/70 mm Hg), heart rate is 110 beats/minute, and respiratory rate is 22 breaths/minute. After she is given a diagnosis of community-acquired pneumonia, she is empirically initiated on ceftriaxone 2 g/day and azithromycin 500 mg/day intravenously. After fluid resuscitation with 6 L of lactated Ringer solution, her blood pressure is unchanged. Dopamine is initiated and titrated to 9 mcg/kg/minute, with a resulting blood pressure of 96/58 mm Hg, and her heart rate is 138 beats/minute. She has made less than 100 mL of urine during the past 6 hours, and her SCr has increased from 0.9 mg/dL to 1.3 mg/dL. Her serum albumin concentration is 2.7 g/dL. Which therapy is best for this patient at this time?
   A. Administer 5% albumin 500 mL intravenously over 1 hour and reassess mean arterial pressure (MAP).
   B. Initiate hydrocortisone 50 mg intravenously every 6 hours.
   C. Change dopamine to norepinephrine 0.01 mcg/kg/minute to maintain a MAP greater than 65 mm Hg.
   D. Reduce the dopamine infusion to 1 mcg/kg/minute to maintain a urine output of at least 1 mL/kg/hour.

4. A 92-year-old woman (weight 51 kg) is admitted to the ICU with urosepsis and septic shock. She lives in a long-term care facility and has a medical history significant for coronary artery disease and hypertension. Her blood pressure is 72/44 mm Hg, central venous pressure (CVP) is 5 mm Hg, heart rate 120 beats/minute, and oxygen saturation (Sa_{O_2}) is 99%; her laboratory values are normal, except for a BUN of 74 mg/dL and Cr of 2.7 mg/dL (baseline of 1.5 mg/dL). Her urine output is about 20 mL/hour. Appropriate empiric antibiotics were initiated. Which therapy is most appropriate to initiate next?
   A. Norepinephrine 0.05 mcg/kg/minute.
   B. Lactated Ringer solution 1500-mL bolus.
   C. Dopamine 5 mcg/kg/minute.
   D. Albumin 5% 500-mL bolus.

5. A 46-year-old man had a witnessed cardiac arrest in an airport terminal. After about 5 minutes, emergency medical services arrived, and defibrillator pads were applied. The cardiac monitor showed ventricular tachycardia (VT), and the patient had no discernible pulse. He was defibrillated with 200 J without return of spontaneous circulation (ROSC). He received an additional two shocks of 200 J with no improvement. Between shocks, the patient received compressions. An intravenous line was obtained, and an epinephrine 1-mg intravenous push was given; chest compressions and artificial

respirations were initiated. Within 1 minute, the patient was reassessed. The cardiac monitor still showed VT, and he remained pulseless; therefore, another shock of 200 J, followed by an amiodarone 300-mg intravenous push, was administered. After this, the patient was converted to a normal sinus rhythm with a heart rate of 100 beats/minute. The patient was then transported to the hospital, intubated and unresponsive. Which recommendation is most likely to improve this patient's outcomes?

A. Administer sodium bicarbonate 50 mEq intravenously.

B. Administer vasopressin 40 units intravenously.

C. Administer a continuous infusion of heparin.

D. Initiate a targeted temperature management protocol.

6. A 72-year-old man is admitted to the medical ICU for post-cardiac arrest care with targeted temperature management. His body temperature was maintained at 91.4°F (33°C) for 24 hours, and the health care team decides it is time to rewarm slowly at 0.5°C every hour. Which is most important to consider during the rewarming phase?

A. Frequent laboratory monitoring is necessary to guide potassium supplementation because of the risk of hypokalemia.

B. A vecuronium continuous infusion should be administered to prevent shivering.

C. Phenytoin should be administered for seizure prophylaxis.

D. Frequent blood glucose monitoring is necessary, given the risk of hypoglycemia.

7. A 65-year-old man with a history of hypothyroidism, heart failure, and myocardial infarction is admitted to the ICU with severe community-acquired pneumonia. Six hours after admission, he develops acute respiratory failure, hypotension, and acute kidney injury from presumed sepsis. He is placed on mechanical ventilation, and a nasogastric tube is placed, with no plans for extubation. Which is most appropriate for this patient's stress ulcer prophylaxis (SUP)?

A. Administer sucralfate 1 g four times daily by nasogastric tube.

B. Administer magnesium hydroxide 30 mL four times daily by nasogastric tube.

C. Administer famotidine 20 mg intravenously daily.

D. No prophylaxis is indicated for this patient because he has no risk factors for SUP.

8. A 45-year-old man is admitted to the ICU with H1N1 influenza causing respiratory failure. He is intubated and sedated with fentanyl 200 mcg/hour and propofol 25 mcg/kg/minute. He has received 4 L of lactated Ringer solution and 1 L of albumin and is currently receiving norepinephrine 0.15 mcg/kg/minute and vasopressin 0.03 unit/minute for hemodynamic support. His current vital signs are blood pressure 85/58 mm Hg, heart rate 99 beats/minute, and respiratory rate 18 breaths/minute. Which is the best plan for this patient's steroid therapy?

A. Initiate hydrocortisone 50 mg every 6 hours intravenously.

B. Perform a cosyntropin stimulation test and initiate hydrocortisone 50 mg every 6 hours intravenously if the patient does not have an increase greater than 9 mcg/dL from baseline.

C. Check a random cortisol and initiate hydrocortisone 50 mg every 6 hours intravenously if the result is less than 10 mcg/dL.

D. Steroids are not indicated at this time.

9. A 19-year-old man (height 71 inches [180 cm], weight 68 kg) is admitted to the ICU after ingesting an unknown quantity of acetaminophen. After initial resuscitation and treatment with acetylcysteine, the patient remains unresponsive and intubated. The intensivist would like to start enteral nutrition (EN) as soon as possible. Which is the best way to calculate the patient's caloric and protein needs?

A. Estimate caloric needs at 25 kcal/kg and protein at 1.2 g/kg.

B. Perform indirect calorimetry to estimate caloric and protein needs.

C. Estimate caloric needs at 14 kcal/kg and protein at 2 g/kg.

D. Calculate caloric needs based on the Mifflin equation, and order a prealbumin concentration to assess protein needs.

10. A 57-year-old woman is admitted to the ICU with injuries sustained after a fall from 12 feet. She has traumatic brain injury and has been intubated for airway protection. What is the best intervention to prevent ventilator-associated pneumonia in this patient?
    A. Initiate pantoprazole 40 mg intravenously daily.
    B. Perform selective digestive decontamination with enteral polymyxin B sulfate, neomycin sulfate, and vancomycin hydrochloride.
    C. Maintain head of bed elevation at 20 degrees at all times.
    D. Start chlorhexidine 0.12% oral swabs twice daily.

11. You are the critical care pharmacist for a 300-bed hospital. The critical care committee wants to institute an evidence-based glucose control protocol for the ICU. What is the best goal to implement for patients who present with septic shock?
    A. Check blood glucose every 6 hours and treat with sliding scale protocol when greater than 180 mg/dL.
    B. Initiate insulin infusion with a target of 110–140 mg/dL for two blood glucose values greater than 140 mg/dL.
    C. Initiate insulin infusion with a target of 140–200 mg/dL for two blood glucose values greater than 180 mg/dL.
    D. Initiate insulin infusion with a target blood glucose of 80–110 mg/dL for two blood glucose values greater than 150 mg/dL.

12. Which is the most appropriate therapy to reduce the risk of delayed ischemia and improve neurologic outcomes after an aneurysmal subarachnoid hemorrhage (SAH)?
    A. Clevidipine continuous infusion titrated to maintain a systolic blood pressure (SBP) less than 160 mm Hg.
    B. Nimodipine 60 mg orally every 4 hours for 21 days.
    C. Norepinephrine continuous infusion titrated to maintain an SBP greater than 160 mm Hg.
    D. Amlodipine 10 mg orally every 24 hours for 21 days.

BPS Pharmacotherapy Specialty Examination Content Outline

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline, tested during the Spring 2024 window:

1. Patient-Centered Pharmacotherapy
   a. 1.1. Develop patient-centered, evidence-based pharmacotherapy plans. Subtasks: 1.1.1 – 1.1.3, 1.1.6, 1.1.8, 1.1.10, 1.1.11, 1.1.14 – 1.1.16.
   b. 1.2. Monitor the patient to ensure safe and effective pharmacotherapy. Subtasks: 1.2.1, 1.2.2, 1.2.4.
   c. 1.3. Modify pharmacotherapy plans through ongoing patient assessment. Subtasks: 1.3.1 – 1.3.5.
2. Application of Evidence to Practice and Education
   a. 2.2. Evaluate pharmacotherapy-related literature and health information. Subtasks: 2.2.1, 2.2.3, 2.2.7 – 2.2.11.
3. Healthcare Systems and Population Health
   a. 3.2. Utilize technology to promote safe and effective medication use. Subtasks: 3.2.1 – 3.2.3.
   b. 3.3. Incorporate public health initiatives to improve population health. Subtask: 3.3.3.

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline, tested starting Fall 2024:

1. Patient Care Specialty Areas
   a. 1A. Primary Pharmacotherapy Specialty Areas. Subtasks: 1A1 – 1A5.
   b. 1B. Secondary Pharmacotherapy Specialty Areas. Subtasks: 1B1, 1B5.
2. Therapeutics and Patient Management
   a. 2A. Treatment Planning. Subtasks: 2A1 – 2A4.
   b. 2B. Therapeutic Implementation. Subtasks: 2B1, 2B3, 2B5.
   c. 2C. Treatment Outcomes and Monitoring. Subtasks: 2C1 – 2C4.
3. Professional Practice
   a. 3A. Quality of Care. Subtasks: 3A1, 3A4.
   b. 3B. Evidence-Based Practice. Subtasks: 3B1, 3B2.
   c. 3C. Practice Management. Subtasks: 3C1, 3C2.

I. INTERPRETATION OF HEMODYNAMIC PARAMETERS

A. Hemodynamics (Table 1)
   1. Arterial blood pressure is the product of cardiac output and resistance to flow (systemic vascular resistance [SVR]).
      a. Cardiac output (milliliters of blood pumped per minute) is calculated by stroke volume (milliliters of blood ejected from the left ventricle per beat) times heart rate.
      b. Stroke volume is determined by preload (amount of blood available to eject), afterload (resistance to ejection), and contractility (amount of force generated by the heart). These will be discussed in more detail later.
   2. Arterial blood pressure can be described by systolic blood pressure (SBP), diastolic blood pressure (DBP), or mean arterial pressure (MAP). This is the driving pressure for organ perfusion and oxygen delivery. MAP = [SBP + (2 × DBP)]/3. Note that MAP is based largely on DBP because most of the cardiac cycle is spent in diastole.
      a. Normal MAP is 70–100 mm Hg.
      b. MAP is an indication of global perfusion pressure; a MAP of at least 65 mm Hg is necessary for adequate cerebral perfusion in most patients.
      c. MAP can be calculated using the above equation, but direct measurement from an arterial line provides more timely and accurate measurements.
   3. Preload is defined as ventricular end-diastolic volume, and it increases proportionally with stroke volume (Frank-Starling mechanism). Commonly used measures of preload include central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), or pulmonary artery occlusion pressure (PAOP), and newer measures such as stroke volume variation (SVV) and pulse pressure variation (PPV).
      a. CVP is the pressure in the vena cava at the point of blood returning to the right atrium and may reflect volume status, although its utility in assessing volume responsiveness (i.e., whether a patient's low blood pressure will improve with an increase in intravascular volume) is poor. A CVP of 8–12 mm Hg (12–16 mm Hg if mechanically ventilated because of increases in thoracic pressure) has been suggested as being optimal for a patient with hypoperfusion from sepsis, but data on the use of CVP are lacking. CVP values at the extremes usually reflect hypovolemia (less than 2 mm Hg) and hypervolemia (greater than 18 mm Hg).
      b. PCWP or PAOP is the pressure when a balloon is inflated (wedged) in one of the pulmonary artery branches. Because the measurement is taken closer to the left ventricle than CVP, it may be a more accurate marker of volume status, but controversy remains. Its utility is diminished because the use of pulmonary artery catheters has severely declined.
      c. Dynamic markers (SVV, PPV) are increasingly used to determine a patient's volume responsiveness to a fluid challenge. These measurements consider other variables and provide a better assessment of an individual patient's position on the Starling curve. Measures of fluid responsiveness include the passive leg raise test, which aims to determine whether venous return and stroke volume increase in response to a fluid bolus followed by raising the patient's lower extremities. Further information about dynamic markers can be found in the references. (Curr Opin Crit Care 2013;19:234-41)

B. Indicators of oxygen delivery
   1. Assessment of end organ function is perhaps the simplest measurement of adequate oxygen delivery. Changes in mental status, decreased urine output (less than 0.5 mL/kg/hour), and cold extremities may be the first markers of organ hypoperfusion.
   2. Blood pressure is the driving force behind oxygen delivery. Every organ is able to autoregulate blood flow, but this ability is generally lost at MAP values less than 65 mm Hg.

3. Lactic acid
   a. Lactic acid is formed during anaerobic metabolism.
   b. During states of hypoperfusion, the tissues receive less blood and therefore less oxygen.
   c. If there is less oxygen for the tissues, they will convert to anaerobic metabolism, with the subsequent production of lactic acid.
   d. Lactate clearance can be used as a therapeutic end point in shock states.
4. Venous oxygen saturation
   a. The oxyhemoglobin saturation of venous blood returning to the right atrium is normally 70%–75% (with a normal [99%–100%] arterial oxygen saturation), indicating that the normal oxygen extraction ratio is around 25%–30%.
   b. In times of decreased oxygen delivery (caused by anemia, a decrease in Sao_2, CO, or tissue perfusion), more oxygen is extracted from the blood that is being perfused to tissues, causing an increased extraction ratio and thus a decrease in venous oxygen saturation.
   c. Central venous oxygen saturation ($Scvo_2$) and mixed venous oxygen saturation (Svo_2) are measurements of venous oxygen saturation. These values are similar, but $Scvo_2$ is slightly higher than Svo_2 because it has not mixed with venous blood from the coronary sinus. $Scvo_2$ is measured in the superior vena cava, and Svo_2 is measured from the pulmonary artery; therefore, Svo_2 is about 5% lower than $Scvo_2$.
   d. A normal Svo_2 does not rule out hypoperfusion in patients with impaired extraction (e.g., sepsis). An elevated lactate concentration may indicate hypoperfusion in this scenario.

Table 1. Hemodynamic Parameters and Normal Values

Parameter	Calculation (If Applicable)	Normal Range
Systolic blood pressure (SBP)		90–140 mm Hg
Diastolic blood pressure (DBP)		60–90 mm Hg
Mean arterial blood pressure (MAP)	[SBP + (2 × DBP)]/3	70–100 mm Hg
Systemic vascular resistance (SVR)	80 [(MAP – CVP)/CO]	800–1200 dynes/s/cm^5
Heart rate (HR)		60–80 beats/min
Cardiac output (CO)	HR × SV	4–7 L/min
Cardiac index (CI)	CO/BSA	2.5–4.2 L/min/m^2
Stroke volume (SV)	CO/HR	60–130 mL/beat
Pulmonary capillary wedge pressure (PCWP) or pulmonary arterial occlusion pressure (PAOP)		5–12 mm Hg
Central venous pressure (CVP)		2–6 mm Hg
Lactic acid		<2 mmol/L
Central venous oxygen saturation ($Scvo_2$)		70%–75%

BSA = body surface area.

II. TREATMENT OF SHOCK

A. Diagnosis of shock is based on hemodynamic parameters. Many patients have more than one type of shock (Table 2).

Table 2. Definitions of Shock

Hemodynamic Subset	CI	CVP/PCWP	SVR	Description
Hypovolemic	Low	Low	High	Gastrointestinal hemorrhage, major bleeding Patients with hypovolemic shock have a low CI because the Starling curve shows reduced cardiac function as intravascular volume is reduced The reduced intravascular volume is indicated by a low PCWP, with a reflex increase in SVR to maintain tissue perfusion SVR is inversely related to flow (CI)
Cardiogenic	Low	High	High	Acute myocardial infarction, acute decompensated heart failure, valvular failure Patients with cardiogenic shock have acute heart failure (low CI) The insufficient forward flow of blood causes venous congestion (high PCWP) and an underfilled arterial blood volume The subsequent reduced tissue perfusion causes a reflex vasoconstriction (which, although it can improve blood flow to vital organs, can worsen heart function by increasing afterload) and reduced renal excretion of Na^+ and water
Obstructive	Low	Low (impaired ejection) High (impaired filling)	High	Embolic events Impairment in diastolic filling (caused by tamponade) or systolic contraction (massive pulmonary embolus, aortic stenosis) Differentiation can usually be made by patient history
Distributive or vasodilatory	High (early) Low (late)	Low (early) Normal to high (late)	Low (early and late)	Sepsis Patients with distributive shock are typically hyperdynamic (high CI), with vasodilation (low SVR) and increased vascular permeability (“leaky capillaries”), causing intravascular fluid to shift into the interstitial spaces (thus, low PCWP) The vasodilation and vascular permeability are attributable to cytokines and inflammatory mediators

CI = cardiac index; CVP = central venous pressure; Na^+ = sodium; PCWP = pulmonary capillary wedge pressure; SVR = systemic vascular resistance.

B. Treatment of hypovolemic shock
   1. Treatment focuses on restoring intravascular volume and oxygen-carrying capacity. Crystalloids and colloids are discussed in the "Fluids, Electrolytes, and Nutrition" chapter.
   2. Blood products (packed red blood cells and coagulation factors) should be administered in hypovolemic shock, if clinically indicated.
      a. A hemoglobin less than 7 g/dL is defined as a transfusion threshold in patients in the general ICU. It is reasonable to have higher hemoglobin targets in selected patients (e.g., patients with symptomatic cardiovascular disease may need a hemoglobin greater than 10 g/dL).
      b. Actively bleeding patients should have blood products administered regardless of hemoglobin concentration in conjunction with interventions to stop the source of bleeding.
   3. Patients may need vasopressors if hypotension is not rapidly reversed with fluid resuscitation.
      a. The efficacy of vasopressors is reduced in patients who have not received adequate intravascular volume resuscitation.
      b. Adverse events associated with vasopressors (e.g., arrhythmias, ischemia) may occur more often or at greater severity in patients who have not received adequate fluid resuscitation.

C. Treatment of cardiogenic shock
   1. Cardiogenic shock involves injury to the left or right ventricle, resulting in reduced cardiac output and perfusion. Causes of myocardial injury are extensive and can be ischemic (e.g., myocardial infarction) and non-ischemic (e.g., myocarditis, valvular disease, medication nonadherence). Injury can be multifactorial and be present with other types of shock.
   2. Management depends on the underlying chronic or acute cardiovascular diseases, and treatment considerations vary depending on the hemodynamic indices. Details are discussed in the "Acute Care in Cardiology" chapter.

D. Treatment of obstructive shock
   1. Fluids and vasopressors can be used temporarily to improve end organ perfusion, but may not improve outcomes.
   2. Treatment of the actual obstruction is the only way to reverse the shock state.
      a. Massive pulmonary embolism: Thrombectomy or administration of systemic or catheter-directed thrombolytics may be indicated if the patient has a high risk of death.
      b. Cardiac tamponade: Removal of fluid in the pericardial sac is the only definitive treatment.

E. Treatment of vasodilatory and distributive shock
   1. Septic shock is the most common cause of vasodilatory shock (Table 3). Other causes such as anaphylaxis, vasoplegia, intoxication, pancreatitis, and neurogenic and endocrine causes will not be discussed in this section.
   2. The hallmark treatments of septic shock are rapid antibiotic administration and fluid resuscitation, ideally within the first hour of hypotension.
   3. The Surviving Sepsis Campaign (SSC) is an initiative to reduce mortality from sepsis and septic shock.

Table 3. Classifications of Sepsis

	Definition	Criteria
Sepsis	Life-threatening organ dysfunction caused by a dysregulated host response to infection	Sepsis screening tools have a wide variation in diagnostic accuracy, but they are important components of the early identification and treatment of patients with sepsis; a variety of clinical variables (signs of infection, vital signs) and tools may be used for screening, (e.g., SIRS, NEWS, or MEWS); notably, the 2021 guidelines recommend against the use of qSOFA as a single screening tool for sepsis Lactate concentrations can also be used as a sepsis screening tool for patients with suspected sepsis
Septic shock	Septic shock is a subset of sepsis in which profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone	Need for vasopressors to maintain MAP ≥ 65 mm Hg *and* lactate > 2 mmol/L despite adequate fluid resuscitation

MAP = mean arterial pressure; MEWS = Modified Early Warning Score; NEWS = National Early Warning Score; qSOFA = quick Sequential Organ Failure Assessment; SIRS = systemic inflammatory response syndrome.

4. SSC hour-1 bundle
    a. The SSC bundle is a group of selected elements of care taken from evidence-based practice guidelines that, when implemented as a group, have a greater effect on outcomes than any individual element.
    b. The SSC recommends the following bundle to be completed within 1 hour for patients presenting with sepsis or septic shock.
        i. Measure baseline lactate concentration.
            (a) Guide resuscitation to normalize lactate in patients with elevated lactate concentrations (especially when greater than 4 mmol/L) as a marker of tissue hypoperfusion.
        ii. Obtain blood cultures before administering antibiotics.
        iii. Administer appropriate broad-spectrum antibiotics depending on the suspected source of infection and likely pathogens and concerns with multidrug resistance.
        iv. Begin administering 30 mL/kg balanced crystalloid for hypotension or lactate 4 mmol/L or greater.
            (a) Albumin can be considered when patients need a substantial amount of crystalloids. There is no evidence that colloids are superior to crystalloids in improving outcomes, and they are more expensive.
            (b) Hydroxyethyl starches (e.g., hetastarch) are not recommended for fluid resuscitation because of an increased risk of acute kidney injury and mortality.
            (c) Administration of large volumes of chloride-rich solutions leads to non-gap metabolic acidosis and acute kidney injury. The use of "balanced crystalloids" (solutions with electrolyte concentrations similar to those of extracellular fluid, such as lactated Ringer solution and Plasmalyte) for volume replacement may lead to less acute kidney injury than the use of other fluids (0.9% sodium chloride). A recent systematic review and meta-analysis found balanced crystalloids were associated with a lower 28- or 30-day mortality than saline in critically ill patients. Specifically, patients with sepsis had similar mortality rates but lower odds of major adverse kidney events within 30 days. Increasing evidence suggests that balanced crystalloids are preferred to saline for fluid resuscitation in critically ill patients (Ann Pharmacother 2020;54:5-13; Intensive Care Med 2021;47:1181-247).

v. Initiate vasopressors if the patient is hypotensive during or after fluid resuscitation to maintain MAP 65 mm Hg or greater (Table 4).
   (a) The goal MAP of 65 mm Hg may be modified depending on patient-specific factors. A higher goal may be appropriate in patients with atherosclerosis or a history of hypertension. The individualized target MAP should correlate with improvement in other clinical parameters (e.g., lactate concentration, mental status, urine output, capillary refill).
   (b) Ideally, vasopressors should be used after restoration of intravascular volume, but in patients with septic shock and hypoperfusion, vasopressors may be necessary during fluid resuscitation to optimize perfusion of vital organs. Once intravascular volume is optimized with fluid resuscitation, vasopressors should be weaned if possible.
   (c) Recently, focus has shifted toward early restrictive (earlier vasopressor initiation) versus liberal (prioritizing administration of higher fluid volumes before starting vasopressors) fluid resuscitation in septic shock. The multicenter CLOVERS trial did not identify a significant difference in 90-day all-cause mortality between treatment groups, but the average time to treatment randomization was approximately 60 hours in both groups (New Engl J Med 2023;388:499-510).
   (d) Vasopressors improve tissue perfusion by increasing blood pressure and/or CO. Few studies have evaluated an improvement in clinical outcomes, but differences in safety profiles have been observed. Therefore, drug selection is based largely on expert opinion, practitioner experience, and patient response.
   (e) Norepinephrine is the initial vasopressor of choice. The SOAP II trial was a multicenter randomized trial of patients requiring vasopressors because of any type of shock. Enrolled patients received either blinded norepinephrine or dopamine. There was no difference in 28-day mortality, but patients receiving dopamine more commonly developed an arrhythmia, required open-label norepinephrine, and required more days with vasopressor support. The study results suggest although norepinephrine does not improve mortality compared with dopamine, it is safer and more effective.
   (f) Vasopressin can be added to norepinephrine if needed. It is usually administered at a fixed dose of 0.03 units/minute. Splanchnic, digital, and cardiac ischemia have been reported at higher doses. The efficacy of vasopressin when added to norepinephrine is similar to that of norepinephrine alone. Vasopressin can have a vasopressor-sparing effect, although mortality is not improved with the combination. The addition of vasopressin earlier (at norepinephrine doses of less than 15 mcg/minute) may be associated with an improvement in outcomes. The exact threshold of when to add vasopressin varies in the literature and remains unclear; however, more recent evidence is indicating a weight-based threshold is more appropriate than a flat dose threshold. The 2021 guidelines suggest initiating vasopressin with a norepinephrine dose range of 0.25–0.5 mcg/kg/minute. Refer to Table 4 for additional vasopressor dosing. The 2021 guidelines suggest limiting parenteral vasopressors to norepinephrine plus vasopressin because of a lack of evidence showing improved outcomes with more than two vasopressors. However, there may be patient-specific instances warranting the use of more than two vasopressors for fluid-refractory septic shock.
   (g) Epinephrine can be added in patients with inadequate MAP levels despite norepinephrine and vasopressin. Caution should be taken with continuous epinephrine, though, as it may produce a transient lactic acidosis, which can confound the assessment of septic shock resolution.

(h) Dopamine is an alternative to norepinephrine, but it is associated with a higher incidence of tachyarrhythmias compared with norepinephrine. Dopamine use should be limited to patients with a low risk of tachyarrhythmias and absolute or relative bradycardia. Low-dose dopamine should not be used for renal protection because evidence does not support this practice. Use of dopamine is also associated with neuroendocrine abnormalities.

(j) Phenylephrine is an alternative to consider in patients with vasopressor-induced tachyarrhythmias or persistent hypotension refractory to other vasopressors.

(j) Use of an arterial catheter for blood pressure measurements is preferred in patients needing vasopressors, because it is a more accurate measurement of arterial pressure (compared with a blood pressure cuff) and allows continuous monitoring.

(k) The 2021 guidelines suggest starting vasopressors peripherally rather than delaying initiation until a central line is secured. If vasopressor therapy is needed beyond a short period (> 6 hours), efforts should be made to obtain central venous access for administration. This helps reduce the risk of extravasation and subsequent tissue ischemia. If extravasation occurs, stop the vasopressor immediately and switch to another site if necessary. Phentolamine (an α-receptor antagonist) can be injected around the site as soon as possible to reduce tissue necrosis. In a phentolamine shortage, other options include nitroglycerin ointment (applied around the site of extravasation every 6 hours) or subcutaneous terbutaline (peripheral vasodilation is mediated through β_2-receptors).

(l) Angiotensin II is a novel vasoactive agent that increases blood pressure in adults with septic or other distributive shock. It is a peptide hormone of the renin-angiotensin-aldosterone system, causing vasoconstriction and increasing aldosterone release, which increases blood pressure. The 2021 guidelines state angiotensin II may be used as an adjunct vasopressor therapy, and acknowledge the limited evidence and clinical experience currently available. Additional studies are needed to confirm the exact role and benefit in septic shock.

vi. If persistent arterial hypotension occurs despite volume resuscitation or initial lactate 4 mmol/L or more, volume status and tissue perfusion should be reassessed by either of the following:

(a) Repeated focused examination including vital signs, cardiopulmonary examination, capillary refill, pulse, and skin findings assess source control.

(b) Two of the following:

(1) CVP measurement

(2) $Scvo_2$ measurement

(3) Bedside cardiovascular ultrasound

(4) Dynamic assessment of fluid responsiveness with passive leg raise or fluid challenge

Table 4. Vasopressors and Inotropes[a]

Drug	Dose	α_1	β_1	β_2	DA	Notes
Norepinephrine	0.01–3 mcg/kg/min	++++	++	0	0	↓ Renal perfusion ↑ SVR, ↑ MAP ↔ to ↑ CO (at high doses) Peripheral ischemia Can induce tachyarrhythmias and myocardial ischemia
Vasopressin	0.03–0.04 unit/min	0	0	0	0	Direct stimulation of smooth muscle V1 vasopressin receptors; peripheral vasoconstriction, no adrenergic activity Theoretically beneficial because of an apparent relative vasopressin deficiency in septic shock, but no evidence of efficacy over other vasopressors (see text) Effective during acidosis and hypoxia because it does not rely on adrenergic receptors Doses ≥ 0.04 unit/min are associated with coronary vasoconstriction and peripheral necrosis Not titrated like traditional vasopressors Prone to dosing errors because of "unit/min"
Epinephrine	0.04–1 mcg/kg/min	+++	++	++	0	Positive inotropic and chronotropic effects can induce tachyarrhythmias and myocardial ischemia Low doses primarily β-adrenergic; escalating doses primarily α-adrenergic Some evidence of reduced splanchnic circulation, which can lead to gut ischemia Increases blood glucose and lactate concentrations (type B lactic acidosis)[b] May be used for refractory hypotension
Phenylephrine	0.5–8 mcg/kg/min	++++	0	0	0	↓ Renal perfusion ↑ SVR, ↑ MAP Pure α-adrenergic agonist with minimal cardiac activity Rapid ↑ SBP and DBP can cause a reflex bradycardia and reduction in CO Can be administered as a rapid bolus for acute hypotension (e.g., intraoperative) or as a continuous infusion.
Dopamine	1–3 mcg/kg/min	+/–	+	+/–	++++	Lower doses cause renal, coronary, mesenteric, and cerebral arterial vasodilation and a natriuretic response Do not use low-dose dopamine for renal protection because evidence does not support this practice Lower inotropic doses can complement the vasoconstrictive effects of norepinephrine Moderate doses can ↑ contractility and SVR Effects on renal blood flow may be lost at higher doses because of predominant α1-vasoconstrictive effects Any dose can induce arrhythmias Any dose can cause endocrine changes (e.g., decreased prolactin, growth hormone, thyroid hormone); however, the clinical significance is unknown Immediate precursor of norepinephrine Prolonged infusions can deplete endogenous norepinephrine stores, resulting in a loss of vasopressor response
	3–10 mcg/kg/min	+	++	0	++	
	10–20 mcg/kg/min	+++	++	0	+	

Table 4. Vasopressors and Inotropes *(Cont'd)*

Drug	Dose	α_1	β_1	β_2	DA	Notes
Dobutamine	2–20 mcg/kg/min	+	+++	+	0	Positive inotrope (↑ CO) Can cause hypotension because of β_2-stimulation Higher doses can cause tachyarrhythmias and changes in BP, which can lead to myocardial ischemia
Milrinone	50-mcg/kg load over 10 min, followed by 0.375–0.75 mcg/kg/min	0	0	0	0	Noncatecholamine, phosphodiesterase type 3 inhibitor Positive inotrope (↑ CO) Vasodilation leading to hypotension, arrhythmias possible Excreted as mostly unchanged drug in urine; renal dose adjustments necessary Loading doses often omitted especially because of increased risk of vasodilation
Angiotensin II	Initial (during first 3 hr of treatment): 10–80 ng/kg/min Maintenance: 1.25–40 ng/kg/min	0	0	0	0	Binds to the G protein-coupled angiotensin receptor type 1 on vascular smooth muscle cells resulting in smooth muscle contraction, and vasoconstriction Increased risk of thrombotic events (mechanical and pharmacologic thromboprophylaxis is recommended) May cause increased heart rate, lactic acidosis, infections (e.g., fungal), and delirium Recent exposure to angiotensin-converting enzyme (ACE) inhibitors may cause an exaggerated response to angiotensin II Recent exposure to angiotensin II receptor blockers (ARBs) may cause a reduced response to angiotensin II

[a]Some vasopressors may be administered using weight-based dosing or non-weight-based dosing (e.g., norepinephrine, epinephrine, phenylephrine).

[b]As opposed to type A lactic acidosis caused by tissue hypoperfusion, epinephrine may cause increased lactate concentrations because of accelerated aerobic glycolysis through β-adrenergic stimulation.

BP = blood pressure; CO = cardiac output; DA = dopamine; DBP = diastolic blood pressure; MAP = mean arterial pressure; SBP = systolic blood pressure; SVR = systemic vascular resistance.

0 = no effect

+/− = may have some effect

+ = mild effect

++ = moderate effect

+++ = strong effect

++++ = strongest effect

↓ = decreases; ↑ = increases; ↔ = no change

5. Appropriate use of antimicrobials in patients with sepsis
    a. Empiric antimicrobials should cover likely pathogens according to suspected location of infection and risk of multidrug-resistant pathogens, such as methicillin-resistant *Staphyloccus aureus* (MRSA) and *Pseudomonas aeruginosa*. Common sources of infection are lung, abdomen, blood, and urinary tract. Please refer to the "Infectious Diseases" chapter for discussion of specific agents.
    b. Consider empiric fungal therapy with either triazoles such as fluconazole, an echinocandin, or a lipid formulation of amphotericin B if patients have several risk factors, including recent abdominal surgery, long-term PN, indwelling central venous catheters, or recent treatment with broad-spectrum antibiotics or if patients are immunocompromised (e.g., chronic corticosteroids or other immunosuppressants, neutropenia, malignancy, organ transplant). An echinocandin is preferred in patients with septic shock, recently treated with antifungal agents, or if *Candida glabrata* or *Candida krusei* infection is suspected.
    c. Other considerations when choosing appropriate antimicrobials include the patient's history of drug allergy or intolerance, recent antibiotic use, comorbidities, and antimicrobial susceptibility patterns in the community and hospital.
    d. Consider empiric antiviral therapy with oseltamivir for patients presenting with flu-like symptoms during flu season.

e. Sepsis secondary to COVID-19 infection was not directly referenced in the 2021 SSC guidelines; however, please reference the COVID-19 section in the Infectious Diseases I chapter for more information.
f. For patients with probable sepsis or shock with a high likelihood from sepsis, antimicrobials should be administered immediately, and ideally within one hour of recognition. For patients with possible sepsis without shock, rapid assessment should be completed to assess for infectious or non-infectious illness. This should be completed within 3 hours of presentation, and antimicrobials should be administered within this time if concern for infection persists. Antimicrobials should be administered preferably after at least two sets of blood cultures (one obtained percutaneously) are obtained. Quantitative cultures of other potential sites of infection (e.g., urine, sputum) should also be obtained before antimicrobials are administered, if possible.
g. If several antibiotics are prescribed, administer the broadest coverage first and infuse as quickly as possible.
h. Mortality increases by 7.6% for each 1-hour delay in administering appropriate antimicrobials at appropriate doses which obtain therapeutic serum concentrations at the suspected infection site.
i. Appropriate antimicrobials do not reduce the importance of emergency source control by drainage, debridement, or device removal as needed.
j. De-escalation should occur with respect to culture data or clinical judgment. Empiric use of combination therapy should not be administered for longer than 3–5 days if de-escalation to a single agent is appropriate.
k. Consider discontinuing antimicrobials after 7-10 days for most serious infections. A longer course may be necessary if the patient has slow response, an undrainable foci, deep seated infections, immunologic deficiencies, bacteremia with *S. aureus*, or some fungal or viral infections.
l. Procalcitonin, a serum biomarker for bacterial infections, can be used as a guide for escalation or de-escalation of antibiotic therapy. However, procalcitonin alone should not be used to determine whether to initiate or discontinue empiric antibiotic therapy. Protocols that encourage or discourage the use of antibiotics depending on procalcitonin concentrations decrease unnecessary antibiotic use without increasing harm to patients. Use of MRSA nasal swabs and other rapid diagnostic test data can also be incorporated into empiric antimicrobial regimens, with de-escalation of broader coverage as indicated.
m. Discontinue antimicrobials if no infectious cause is found.

6. Indication for and use of corticosteroids
   a. Adrenal function in critically ill patients can be suppressed by endotoxins produced by bacteria and by the body's immune response to stress.
   b. Early studies showed a relationship between vasopressor responsiveness and glucocorticoid administration.
   c. The use of a corticotropin stimulation test ("stim test") is no longer recommended.
      i. The corticotropin stimulation test has come under criticism because of the high dose of cosyntropin administered, the inability to measure free (active) cortisol, and lack of data on outcomes of responders versus nonresponders. It is not indicated for evaluation of immune response in the general ICU septic population.
   d. Clinical trials of steroids in septic shock
      i. In a study published in 2002, adult patients with septic shock were given a corticotropin stimulation test and then randomly assigned to intravenous hydrocortisone combined with oral fludrocortisone or placebo, regardless of stimulation test results. In the entire patient population, steroid therapy improved 28-day survival; however, this result was driven primarily by a mortality benefit in patients who were unresponsive to the corticotropin stimulation test. Responders showed no improvement with steroid therapy (JAMA 2002;288:862-70).

ii. In the CORTICUS trial, published in 2008, corticosteroids were not associated with a mortality benefit regardless of the results from a corticotropin stimulation test; however, they were associated with a higher risk of hyperglycemia, new sepsis, or septic shock. For this reason, corticosteroids are not recommended in patients with septic shock who have been stabilized with fluid and vasopressor therapy.

iii. In the ADRENAL trial, published in 2018, adult patients with septic shock were randomized to receive an intravenous infusion of hydrocortisone or placebo. There was no difference in 90-day all cause mortality, but hydrocortisone infusion decreased duration of septic shock and blood transfusions. This is the largest randomized controlled trial assessing steroids in septic shock.

iv. The APROCCHSS Trial, also published in 2018, used intravenous hydrocortisone and oral fludrocortisone or placebo. There was a decrease in 90-day all cause mortality and duration of septic shock in patients treated with hydrocortisone and fludrocortisone.

v. The mixed results from numerous studies leaves uncertainty as to the mortality benefit of steroids in septic shock. However, there seems to be consistency as to the short-term benefits including decreased time to resolution of shock especially relative to start of supplementation.

vi. Tapering systemic steroids is generally recommended following longer exposures to corticosteroids, given the likelihood of producing critical illness-related corticosteroid insufficiency (Crit Care Med 2008;36:1937-49).

e. Evidence-based guidelines

i. SSC guidelines

(a) The SSC suggests the use of intravenous corticosteroids for adult patients with septic shock and ongoing requirement for vasopressor therapy. Hydrocortisone 200 mg per day is recommended based on multiple studies, and it may be administered either as a continuous infusion or 50 mg intravenously every 6 hours. Although the optimal timing of initiation is uncertain, the 2021 guidelines define ongoing requirement of vasopressor therapy as norepinephrine greater than 0.25 mcg/kg/min for at least 4 hours. There is growing literature that early initiation of hydrocortisone in this patient population may be associated with improved outcomes such as shorter duration of vasopressor therapy.

(b) The SSC recommends against using the corticotropin stimulation test to identify the subset of adults with septic shock who should receive hydrocortisone.

(c) Although fludrocortisone was a component of the treatment regimen in some studies, the SSC only includes hydrocortisone in recommendations for septic shock.

ii. American College of Critical Care Medicine corticosteroid insufficiency guidelines recognize that although hypothalamic-pituitary-adrenal axis dysfunction is common in some critically ill patients (sepsis), diagnosis and management of this disorder are complicated.

(a) The expert panel's recommendations for septic shock are similar to the SSC guidelines, and hydrocortisone should be considered in the management strategy for patients with septic shock, particularly those who have responded poorly to fluid resuscitation and vasopressor agents.

(b) Furthermore, the corticotropin stimulation test should not be used to identify patients with septic shock or acute respiratory distress syndrome (ARDS) who should receive glucocorticoids.

(c) Patients should be weaned off steroid therapy once vasopressors are no longer necessary.

7. Metabolic resuscitation

a. High-dose intravenous ascorbic acid (vitamin C) has anti-inflammatory and antioxidant properties that may be beneficial in sepsis.

b. Thiamine deficiency occurs in critically ill patients with sepsis, and supplementation in these patients improves lactate clearance.

c. Ascorbic acid and hydrocortisone may have synergistic protective effects on the vascular endothelium.
d. A single-center, retrospective before-and-after study assessed coadministration of hydrocortisone, high-dose ascorbic acid, and thiamine (HAT) therapy for patients with severe sepsis or septic shock. HAT therapy was associated with a shorter duration of vasopressors and a 31.9% decrease in hospital mortality. However, other studies assessing hydrocortisone alone (described in the previous section) have consistently shown decreased time to resolution of septic shock and inconsistently shown improved mortality rates. Therefore, it is unclear whether the benefit was a result of HAT therapy or of hydrocortisone alone (Chest 2017;151:1229-38).
e. Several randomized controlled trials were subsequently published that failed to reproduce the mortality benefit with HAT therapy. The VITAMINS trial compared HAT therapy with hydrocortisone alone. Results showed no improvement in the duration of time alive and free of vasopressor administration over 7 days (JAMA 2020;323:423-31). The VICTAS trial compared HAT therapy with placebo and found no difference in ventilator-free and vasopressor-free days and no difference in 30-day mortality (JAMA 2021;325:742-50).
f. Although these trials had notable limitations, each suggest that HAT therapy should not be routinely administered in sepsis. The 2021 guidelines suggest against the use of ascorbic acid for adults with sepsis or septic shock.

III. INTERPRETATION OF ACID-BASE DISTURBANCES

A. Normal Arterial Blood Gas Values

pH	7.40 (range 7.35–7.45)
P_{CO_2}	35–45 mm Hg
P_{O_2}	80–100 mm Hg
HCO_3^-	22–26 mEq/L (or mmol/L)
Sa_{O_2}	95%–100%

B. Acidemia: Any pH less than 7.35 indicates a primary acidosis.

C. Alkalemia: Any pH greater than 7.45 indicates a primary alkalosis.

D. Metabolic disorders
   1. Acidosis: Decreased HCO_3^-
   2. Alkalosis: Increased HCO_3^-

E. Respiratory disorders
   1. Acidosis: Increased P_{CO_2}
   2. Alkalosis: Decreased P_{CO_2}

F. Compensation: Occurs in an attempt to normalize the pH in response to the primary problem (Table 5)
   1. Respiratory compensation occurs immediately with changes in respiratory rate.
      a. The compensation for metabolic acidosis is respiratory alkalosis (i.e., decrease in P_{CO_2}). This is achieved by increasing the respiratory rate to eliminate more CO_2, thus making pH more basic (i.e., higher pH).
      b. The compensation for metabolic alkalosis is a respiratory acidosis (i.e., increase in P_{CO_2}). This is achieved by slowing the respiratory rate to retain more CO_2, thus making pH more acidic (i.e., lower pH).
   2. Metabolic compensation occurs slowly in the kidneys by regulating the excretion and reabsorption of HCO_3^- and H^+.
      a. The compensation for a respiratory acidosis is metabolic alkalosis (i.e., an increase in HCO_3^-).
      b. The compensation for a respiratory alkalosis is metabolic acidosis (i.e., a decrease in HCO_3^-).

Table 5. Predicted Degrees of Compensation in Acid-Base Disturbances

Normal Values **HCO_3^- = 24 mmol/L** **P_{CO_2} = 40 mm Hg**	**Primary Disturbance**	**Compensation**
Metabolic acidosis	↓ HCO_3^- by 1 mmol/L	↓ P_{CO_2} by 1.2 mm Hg
Metabolic alkalosis	↑ HCO_3^- by 1 mmol/L	↑ P_{CO_2} by 0.7 mm Hg
Respiratory acidosis Acute Chronic (>3 days)	 ↑ P_{CO_2} by 10 mm Hg ↑ P_{CO_2} by 10 mm Hg	 ↑ HCO_3^- by 1 mmol/L ↑ HCO_3^- by 3.5 mmol/L
Respiratory alkalosis Acute Chronic (>3 days)	 ↓ P_{CO_2} by 10 mm Hg ↓ P_{CO_2} by 10 mm Hg	 ↓ HCO_3^- = 2 mmol/L ↓ HCO_3^- = 4 mmol/L

G. Steps to evaluate acid-base disorders (Table 6)
   1. Assess pH, P_{CO_2}, and HCO_3^-.
      a. Acidemia if pH less than 7.35
         i. If P_{CO_2} is elevated, the primary disorder is respiratory acidosis.
         ii. If HCO_3^- is decreased, the primary disorder is metabolic acidosis.
      b. Alkalemia if pH is greater than 7.45
         i. If P_{CO_2} is decreased, the primary disorder is respiratory alkalosis.
         ii. If HCO_3^- is elevated, the primary disorder is metabolic alkalosis.
   2. Calculate the anion gap (AG) = $[Na+] - [Cl^- + HCO_3^-]$.
      a. Normal range is 6–12 mEq/L.
      b. If AG is more than 12, there is a primary metabolic acidosis regardless of pH or HCO_3^-. Some patients have a mixed acid-base disorder in which they have more than one primary disorder.
      c. Hypoalbuminemia decreases the AG by 2.5–3 mEq/L for every 1-g/dL decrease in serum albumin less than 4 g/dL.
   3. Calculate the excess AG = Total AG − Normal AG. Add excess AG to serum bicarbonate.
      a. If the sum is greater than a normal serum bicarbonate (i.e., more than 26 mEq/L), there is also an AG metabolic alkalosis (this can occur in addition to other primary disorders).
      b. If the sum is less than a normal serum bicarbonate (i.e., less than 22 mEq/L), there is an underlying non-AG metabolic acidosis.

Table 6. Causes of Acid-Base Disturbances

	Respiratory Acidosis	Respiratory Alkalosis	Metabolic Acidosis	Metabolic Alkalosis
Etiology	Pulmonary edema Cardiac arrest CNS depression Stroke Pulmonary embolus Pneumonia Bronchospasm Spinal cord injury Sedatives	Anxiety Pain CNS tumor Stroke Head injury Hypoxia Stimulant drugs Reduced oxygen-carrying capacity Reduced alveolar oxygen extraction Respiratory rate stimulation Extracorporeal removal	**Anion gap** (MUDPILES) Methanol Uremia DKA Propylene glycol Intoxication or infection Lactic acidosis Ethylene glycol Salicylate **Non–anion gap** (F-USED CARS) Fistula (pancreatic) Uteroenteric conduits Saline excess Endocrine (hyperparathyroid) Diarrhea Carbonic anhydrase inhibitors Arginine, lysine, Cl^- Renal tubular acidosis Spironolactone	**Urine Cl^- > 25** (Chloride resistant) Hyperaldosteronism ↑ Mineralocorticoid **Urine Cl^- < 25** (Chloride responsive) Vomiting NG suction Diuretic
Treatment	Correct cause Invasive/noninvasive ventilation	Correct cause Oxygen supplementation Invasive/noninvasive ventilation Hypoventilation Sedation	Correct cause Base use in AG metabolic acidosis is controversial (Sodium bicarbonate has traditionally been used, but evidence of clinical benefit is lacking) Use of bases (sodium bicarbonate or THAM) may be considered in non-AG metabolic acidosis	Correct cause **If urine Cl^- > 25** Potassium Aldosterone antagonist Acetazolamide **If urine Cl^- < 25** 0.9% NaCl Consider acetazolamide Consider HCl (if severe)

AG = anion gap; Cl^- = chloride; CNS = central nervous system; DKA = diabetic ketoacidosis; HCl = hydrochloric acid; NaCl = sodium chloride; NG = nasogastric; THAM = tromethamine or tris-hydroxymethyl aminomethane.

Patient Cases

1. A 62-year-old woman has been hospitalized in the ICU for several weeks. Her hospital stay has been complicated by aspiration pneumonia and sepsis, necessitating prolonged courses of antibiotics. For the past few days, she has been having high temperatures, and her stool output has increased dramatically. Her most recent stool samples have tested positive for *Clostridioides difficile* toxin, and her laboratory tests show serum sodium 138 mEq/L, K 3.5 mEq/L, Cl 115 mEq/L, HCO_3^- 15 mEq/L, albumin 4.4 g/dL, pH 7.32, and $Paco_2$ 30 mm Hg. Which is most consistent with this patient's primary acid-base disturbance?

   A. AG metabolic acidosis.

   B. Non-AG metabolic acidosis.

   C. Chloride-responsive metabolic alkalosis.

   D. Acute respiratory acidosis.

2. A 32-year-old man with no pertinent medical history is admitted to the hospital after being "found down" in his home with an empty bottle of alprazolam by his side. On arrival at the emergency department, he was neurologically unresponsive, with the following ABG values: pH 7.21, $Paco_2$ 58 mm Hg, Pao_2 90 mm Hg, HCO_3- 24 mEq/L, and Sao_2 86% on 2 L/minute of oxygen by nasal cannula. Which action is most appropriate?

   A. Administer acetazolamide 500 mg intravenous push.

   B. Administer 100% oxygen by face mask.

   C. Give sodium bicarbonate 100 mEq intravenous push.

   D. Provide urgent intubation.

3. A 55-year-old woman is admitted to the hospital after several days of worsening shortness of breath. Recently, she was discharged from the hospital after a similar episode and was doing fine until 3 days before admission, when she developed a productive cough, necessitating an increase in her home oxygen and more frequent use of her metered dose inhalers. On admission to the medical ICU, she was anxious and markedly distressed, with rapid, shallow breaths. She was hypertensive (160/80 mm Hg), tachycardic (140 beats/minute), and tachypneic (respiratory rate 28 breaths/minute). Her ABG showed pH 7.30, $Paco_2$ 59 mm Hg, Pao_2 50 mm Hg, HCO_3- 28 mEq/L, and Sao_2 83% on 6 L/minute of oxygen by face mask, and she was immediately intubated. Her most recent laboratory tests show serum sodium 142 mEq/L, K 3.8 mEq/L, Cl 109 mEq/L, HCO_3- 28 mEq/L, and albumin 4.1 g/dL. Which primary acid-base disturbance is most consistent with this patient's presentation and laboratory data?

   A. AG metabolic acidosis.

   B. Non-AG metabolic acidosis

   C. Respiratory acidosis.

   D. Respiratory alkalosis.

Patient Cases *(Cont'd)*

4. A 65-year-old woman is admitted to cardiac surgery ICU after an aortic valve replacement. On hospital day 4, she is hypotensive (blood pressure 80/50 mm Hg), tachycardic (heart rate 125 beats/minute), tachypneic (respiratory rate 30 breaths/minute), hypoxemic (Pao_2 40 mm Hg), febrile (temperature 103.1°F [39.5°C]), and confused. The patient is given adequate boluses of lactated Ringer solution and is then intubated and initiated on piperacillin/tazobactam and vancomycin for possible nosocomial pneumonia. After fluid boluses fail to improve her hemodynamic and clinical status, a pulmonary artery catheter is placed, which reveals a PCWP of 18 mm Hg, CI of 3.3 L/minute/m^2 and SVR of 515 dynes/second/cm^5. Her chest radiograph reveals a left lower lobe consolidation, and she still needs 100% fraction of inspired oxygen (FiO_2). Which action is best?

   A. Administer angiotensin II infusion titrated to achieve a MAP of at least 65 mm Hg.

   B. Administer a dobutamine infusion titrated to achieve a MAP of at least 65 mm Hg.

   C. Administer a norepinephrine infusion titrated to achieve a MAP of at least 65 mm Hg.

   D. Administer a dopamine infusion titrated to achieve a MAP of at least 65 mm Hg.

5. A patient (weight 75 kg) is to be initiated on a continuous infusion of norepinephrine for blood pressure support because of septic shock. The nurse has a 250-mL bag of normal saline containing 4 mg of norepinephrine. Which rate is most appropriate to infuse the norepinephrine drip at a dose of 0.05 mcg/kg/minute?

   A. 7 mL/hour.

   B. 14 mL/hour.

   C. 31.5 mL/hour.

   D. 79 mL/hour.

6. A 42-year-old man was found unresponsive at his group home covered in vomit. He was intubated by the paramedics. On arrival at the emergency department, his blood pressure is 72/30 mm Hg and heart rate is 95 beats/minute. During the next few hours, he receives 5 L of lactated Ringer solution, 500 mL of 5% albumin, and norepinephrine infusing at 0.5 mcg/kg/minute. With these interventions, his blood pressure is 87/56 mm Hg and heart rate is 148 beats/minute. Pertinent laboratory values include WBC 20×10^3 cells/mm^3, lactic acid 1.5 mmol/L, aspartate aminotransferase 78 units/L, SCr 2.2 (baseline 1) mg/dL, platelet count 118,000 cells/mm^3, international normalized ratio (INR) 1.4, and urine output about 45 mL/hour since arrival. Which is the most appropriate intervention at this time?

   A. Add hydrocortisone 50 mg intravenously every 6 hours.

   B. Change norepinephrine infusion to phenylephrine infusion.

   C. Change norepinephrine infusion to dopamine infusion.

   D. Administer 1 L of lactated Ringer solution.

IV. CARDIAC ARREST

A. Training: Any pharmacist who participates in codes should complete basic life support (BLS) and advanced cardiac life support (ACLS) training. The information presented in this section consists of selected highlights from these training sessions; it should not be used in place of a comprehensive training program.

B. 2020 American Heart Association (AHA) Guidelines
   1. Medications used during ACLS: See "Acute Care in Cardiology" chapter for information on drugs, indications, and dosages.
   2. CAB (compressions, airway, breathing): In an unresponsive patient or a patient who is not breathing, one rescuer should initiate a cycle of 30 chest compressions as soon as possible, followed immediately by 2 rescue breaths. After placement of an advanced airway, it may be reasonable for the provider to deliver 1 breath every 6 seconds (10 breaths/minute) while continuous chest compressions are being performed.
   3. Emphasis is on high-quality cardiopulmonary resuscitation (CPR), with a compression rate of 100–120 compressions/minute at a depth of at least 2 inches for adults, and allow complete chest recoil.
   4. For ventricular fibrillation or pulseless ventricular tachycardia, electrical therapy (by an automated external defibrillator or defibrillator) should be initiated as soon as it is available.
   5. For nonshockable rhythms (i.e., pulseless electrical activity, asystole), epinephrine should be administered as soon as possible.
   6. Interruptions in chest compressions should be minimal and no longer than 10 seconds. Chest compressions and defibrillation should not be interrupted for vascular access, medication administration, or airway placement.
   7. End-tidal carbon dioxide ($EtCO_2$) is the partial pressure of exhaled carbon dioxide at the end of expiration. It is measured using waveform capnography. During cardiac arrest, $EtCO_2$ levels reflect the cardiac output generated by chest compressions and myocardial blood flow. $EtCO_2$ levels less than 10 mm Hg immediately after intubation and 20 minutes after initial resuscitation are associated with poor chances of return of spontaneous circulation (ROSC) and survival.
   8. Vasopressin alone or vasopressin with methylprednisolone in combination with epinephrine may be considered in cardiac arrest but offers no advantage as a substitute for epinephrine (Circulation 2024;149:e254-73).
   9. Medication administration
      a. Central venous administration is preferred.
      b. If medications are administered through a peripheral vein, it is important to follow the medication with 20 mL of intravenous fluid to facilitate drug flow from the extremity to the central circulation.
      c. Intraosseous administration is preferred to endotracheal administration if intravenous administration is not possible because of its more predictable drug delivery and pharmacologic effect.
      d. Endotracheal drug administration can be performed by administering 2–2.5 times the standard intravenous dose and diluting in 5–10 mL of sterile water. The following drugs can be administered through an endotracheal tube: naloxone, atropine, epinephrine, lidocaine.

C. Post–cardiac arrest care
   1. After ROSC, systematic post–cardiac arrest care can improve survival and quality of life.
   2. Initial therapy should optimize ventilation, oxygenation, and blood pressure.
      a. Sao_2 should be maintained at 94% or higher.
         i. Insertion of an advanced airway may be necessary.
         ii. Hyperventilation and excess oxygen delivery are harmful and should be avoided, especially after ROSC.
      b. Hypotension (SBP of 90 mm Hg or less) should be treated with fluid boluses and vasopressors if necessary.

3. Avoidance of hyperthermia is recommended because fever in patients after cardiac arrest is associated with poor neurologic outcomes.
4. Targeted temperature management (TTM)
    a. The AHA guidelines recommend that all comatose adult patients with ROSC have targeted temperature management for at least 24 hours beginning as soon as possible after ROSC to improve mortality and neurologic recovery. One study (N Engl J Med 2013;369:2197-206) has shown that a standard target temperature (33°C) does not confer a benefit over a higher target temperature (36°C). A single-center, retrospective, before-and-after cohort study showed that 33°C was associated with a 79% increased odds of neurologically intact survival to discharge compared with 36°C but no difference in hospital mortality. However, those in the 33°C group were cooled faster (1.9 hours vs. 3.5 hours, $p<0.001$), which is a notable limitation that may have affected the results (Crit Care Med 2020;48:362-9). The AHA guidelines allow the clinician to select the exact target temperature. The 2023 post-cardiac arrest guideline updates recommend selecting and maintaining a constant temperature between 32°C and 37.5°C during post-arrest temperature control. Previous guidelines recommended a goal range of 32°C–36°C; however, additional large randomized controlled trials have shown no difference in mortality at higher temperature range. There remains insufficient evidence to recommend specific therapeutic temperature goals for different subgroups of cardiac arrest patients. These results suggest the benefit may be due to avoidance of fever rather than hypothermia.
    b. No single method for inducing hypothermia is recommended over another. Surface cooling devices, endovascular catheters, cooling blankets, ice packs, and cold intravenous fluids can be used. These methods differ in nursing workload, incidence of adverse events, time to target temperature and cost.
    c. Core temperature should be monitored continuously.
    d. Many patients will need sedation and analgesia during periods of hypothermia.
    e. Rewarming should be done slowly (0.3°C–0.5°C every hour) over at least 24 hours, and patients should remain afebrile.
    f. Complications
        i. Shivering
            (a) Shivering causes excess heat production, increased oxygen consumption, and a general stress response; it should be treated and prevented.
            (b) Shivering can be prevented and treated with sedatives (dexmedetomidine, ketamine), anesthetics, analgesics (e.g., meperidine, fentanyl, tramadol), dexamethasone, clonidine, magnesium, ondansetron, buspirone, and paralytics (refer to Crit Care Med 2012;40:3070-82 for individual drugs and doses).
            (c) Note that shivering can be treated without the use of paralytics in many patients. Therefore, paralytics are not mandatory and should be avoided if possible (see disadvantages of paralytics in section VI: Pain, Agitation, Delirium, and Neuromuscular Blockade). Paralytics may be most beneficial during the induction of hypothermia and during rewarming (when risk of shivering is greatest); however, they should be continually reevaluated and discontinued, if possible, once goal temperature is achieved. Pharmacologic antishivering protocols significantly reduce the incidence of shivering and the need for medications that may interfere with neurologic examinations.
        ii. Altered drug metabolism
            (a) Drug clearance is typically reduced during hypothermia, including a depressed activity of cytochrome P450 (CYP) 3A4 and 3A5 hepatic enzymes. Hypothermia can also affect the distribution of drugs to their site of action (e.g., propofol). These effects become more pronounced at cooler temperatures.
            (b) Use bolus dosing during hypothermia induction, and reduce maintenance doses of sedatives (e.g., midazolam, propofol), opiates (fentanyl, remifentanil), phenobarbital, phenytoin, paralytics, and other drugs as needed (refer to review article Crit Care Med 2007;35:2196-204).

iii. Coagulopathy
   (a) Providers may choose not to cool patients with preexisting coagulopathy because of the increased risk of bleeding.
iv. Increased renal excretion of water and subsequent volume depletion
   (a) Renal blood flow tends to decrease during hypothermia; however, mild hypothermia may actually increase renal excretion of water and predispose patients toward dehydration.
v. Arrhythmia and hypotension
   (a) Usually bradycardia
   (b) Discontinue or slightly warm patient if life-threatening arrhythmias or persistent hemodynamic instability develops.
vi. Hyperglycemia and hypoglycemia
   (a) Hyperglycemia during hypothermia, hypoglycemia during rewarming.
   (b) Monitor blood glucose often (i.e., every 1–2 hours) and adjust insulin accordingly.
vii. Infection
   (a) Hypothermia inhibits cytokine production and impairs leukocyte and phagocyte migration, predisposing patients toward infections (J Cardiovasc Thorac Res 2014;6:1-8).
viii. Electrolyte disturbances
   (a) Reductions in K, magnesium, and phosphate during cooling
   (b) Hyperkalemia during rewarming
   (c) Special electrolyte replacement protocols should be used to ensure that patients do not receive too much potassium during cooling such that they are hyperkalemic during rewarming. Electrolyte shifts occur during the induction and rewarming phases of TTM. Frequent monitoring and careful repletion is important to prevent complications from electrolyte abnormalities.

Patient Case

7. A 61-year-old woman collapses in front of her family members, who call 9-1-1 and begin CPR. The paramedics arrive and find the victim unresponsive, with an electrocardiogram revealing ventricular fibrillation, and administer two additional rounds of CPR and two defibrillations, which are successful. In the emergency department, the patient's MAP is 68 mm Hg after fluids and norepinephrine, but the patient remains unresponsive. She is initiated on a TTM protocol. After 24 hours of TTM (body temperature 37°C), the patient is in the ICU, and the rewarming process has recently begun. The pharmacist arrives in the ICU about 30 minutes into the rewarming process. The patient has been receiving a continuous infusion of insulin throughout the period of TTM at an average rate of 4 units/hour, with blood glucose testing every 3 hours. The patient has been sedated with a continuous infusion of propofol and fentanyl and is receiving cisatracurium for neuromuscular blockade. The patient's vital signs are stable, and her laboratory values are normal. Which pharmacist recommendation is most appropriate at this time?

   A. Increase blood glucose testing to now and every 1–2 hours during rewarming.
   B. Adjust cisatracurium infusion to achieve a TOF of 0/4 impulses.
   C. Discontinue propofol infusion to facilitate extubation.
   D. Increase insulin infusion to prevent hyperkalemia.

V. ACUTE RESPIRATORY FAILURE

A. Causes of respiratory failure (Table 7)

Table 7. Respiratory Failure

Indication for Mechanical Ventilation	Examples
Hypoventilation (hypercapnic respiratory failure)	Drug overdose Neuromuscular disease Cardiopulmonary resuscitation Central nervous system injury or disease
Hypoxemia (hypoxic respiratory failure)	Pulmonary injury or disease Pneumonia Pulmonary edema Pulmonary embolus Acute respiratory distress syndrome
Inability to maintain airway	Loss of airway patency (mechanical obstruction, tracheal or chest wall injury) Loss of gag or cough reflex with large-volume aspiration risk (e.g., central nervous system injury, central nervous system depression, cardiovascular accident, seizures, cardiac arrest)

B. Common complications associated with mechanical ventilation (see individual sections later in text for prevention of these complications)
   1. Ventilator-associated pneumonia
   2. Stress ulcers
   3. Venous thrombosis

VI. PAIN, AGITATION, DELIRIUM, AND NEUROMUSCULAR BLOCKADE

A. General considerations
   1. Nonpharmacologic strategies to improve patient comfort include normalizing their environment: lighting, music, massage, verbal reassurance, avoidance of sleep deprivation, and patient positioning based on patient preferences.
   2. Determine patient goals using validated scales and routinely assess pain and sedation.
      a. Routine assessment of pain and sedation should be performed in every patient in the ICU.
         i. Self-reporting is preferred to pain scales for assessing pain in patients who are able to communicate.
         ii. To assess pain in patients who are unable to communicate, the Behavioral Pain Scale (BPS; Table 8) and the Critical-Care Pain Observation Tool (CPOT; Table 9) are recommended because, compared with other scores, they are more valid and reliable for monitoring pain in adult patients in the ICU (except those with brain injury).
            (a) The total BPS score can range from 3 (no pain) to 12 (maximum pain). A score of 6 or higher is generally considered to reflect significant pain.
            (b) The total CPOT score can range from 0 to 8. A score of 3 or higher is generally considered to reflect significant pain.

Table 8. The Behavioral Pain Scale

Item	Description	Score
Facial expression	Relaxed Partially tightened (e.g., brow lowering) Fully tightened (e.g., eyelid closing) Grimacing	1 2 3 4
Upper limb movements	No movement Partially bent Fully bent with finger flexion Permanently retracted	1 2 3 4
Compliance with mechanical ventilation	Tolerating movement Coughing but tolerating ventilation for most of the time Fighting ventilator Unable to control ventilation	1 2 3 4

Adapted from: Payen JF, Bru O, Bosson JL, et al. Assessing pain in critically ill sedated patients by using a behavioral pain scale. Crit Care Med 2001;29:2258-63.

Table 9. Critical Care Pain Observation Tool

Indicator	Description	Score
Facial expression	No muscular tension observed	Relaxed, neutral: 0
	Presence of frowning, brow lowering, orbit tightening, and levator contraction	Tense: 1
	All the above facial movements plus eyelids tightly closed	Grimacing: 2
Body movements	Does not move at all (does not necessarily mean absence of pain)	Absence of movement: 0
	Slow, cautious movements; touching or rubbing the pain site; seeking attention through movements	Protection: 1
	Pulling tube, trying to sit up, moving limbs or thrashing, not following commands, striking at staff, trying to climb out of bed	Restlessness: 2
Muscle tension	No resistance to passive movements	Relaxed: 0
	Resistance to passive movements	Tense, rigid: 1
	Strong resistance to passive movements, inability to complete them	Very tense or rigid: 2
Compliance with the ventilator	Alarms not activated, easy ventilation	Tolerating ventilator or movement: 0
	Alarms stop spontaneously	Coughing but tolerating: 1
	Asynchrony: blocking ventilation, alarms frequently activated	Fighting ventilator: 2
Vocalization (extubated patients)	Talking in normal tone or no sound	Talking in normal tone or no sound: 0
	Sighing, moaning	Sighing, moaning: 1
	Crying out, sobbing	Crying out, sobbing: 2

Adapted from: Gélinas C, Fillion L, Puntillo KA, et al. Validation of the critical-care pain observation tool in adult patients. Am J Crit Care 2006;15:420-7.

iii. Vital signs (e.g., elevated heart rate or blood pressure) indicate further assessment of pain is necessary in adult patients in the ICU.

iv. To assess sedation, the Richmond Agitation-Sedation Scale (RASS; Table 10) and Sedation-Agitation Scale (SAS; Table 11) are recommended because, compared with other sedation scores, they are more valid and reliable for monitoring the quality and depth of sedation in adult ICU patients. Goal sedation scores should be individualized for each patient, but generally, a RASS score of 0 to –2 or an SAS score of 3 or 4 is recommended.

Table 10. Richmond Agitation-Sedation Scale

Scale	Term	Description
+4	Combative	Combative, violent, immediate danger to staff members
+3	Very agitated	Pulls to remove tubes or catheters; aggressive
+2	Agitated	Frequent nonpurposeful movement, fights ventilator
+1	Restless	Anxious but movements not aggressive
0	Alert and calm	Spontaneously pays attention to caregiver
–1	Drowsy	Not fully alert but has sustained awakening to voice (eye opening and eye contact for ≥10 s)
–2	Light sedation	Briefly (<10 s) awakens with eye contact to voice
–3	Moderate sedation	Movement or eye opening to voice but no eye contact
–4	Deep sedation	No response to voice but movement or eye opening to physical stimulation
–5	Unarousable	No response to voice or physical stimulation

Information from: Pun B, Dunn J. The sedation of critically ill adults: part 1. Assessment. Am J Nurs 2007;107:40-8.

Table 11. Sedation-Agitation Scale

Score	Term	Description
7	Dangerous agitation	Pulling at endotracheal tube, trying to remove catheters, climbing over bedrail, striking at staff, thrashing side to side
6	Very agitated	Requiring restraint and frequent verbal reminding of limits, biting endotracheal tube
5	Agitated	Anxious or physically agitated, calms to verbal instructions
4	Calm and cooperative	Calm, easily roused, follows commands
3	Sedated	Difficult to arouse but awakens to verbal stimuli or gentle shaking, follows simple commands but drifts off again
2	Very sedated	Arouses to physical stimuli but does not communicate or follow commands, may move spontaneously
1	Unarousable	Minimal or no response to noxious stimuli, does not communicate or follow commands

Information from: Pun B, Dunn J. The sedation of critically ill adults: part 1. Assessment. Am J Nurs 2007;107:40-8.

b. Pain and discomfort are primary causes of agitation; therefore, treat pain first and add a sedative if needed. This is often referred to as analgosedation.
   i. Use bolus dose analgesics and/or nonpharmacologic interventions before potentially painful procedures.
   ii. Opioid analgesics are considered first line for the treatment of nonneuropathic pain. Gabapentin or carbamazepine can be considered for neuropathic pain. However, gabapentin is typically preferred because of the adverse effects and drug interactions associated with carbamazepine.
   iii. Nonopioid analgesics (e.g., acetaminophen, ketamine) can be used in conjunction with opioids as a "multimodal analgesia" approach to optimize pain control and to avoid dose-related adverse effects.
   iv. Nonsteroidal anti-inflammatory drugs are usually avoided because of the risk of bleeding and kidney injury in critically ill patients.
   v. Nonbenzodiazepine sedatives are preferred to benzodiazepines to improve clinical outcomes in mechanically ventilated patients, especially considering the deleriogenic potential of benzodiazepines.

c. Dosing strategies for analgesics and sedatives
   i. Analgesics and sedatives should be dosed to achieve pain and sedation goals. Adjust sedative medications to achieve a light level of sedation (RASS 0 to –2). Light sedation is needed to allow for patient interaction to evaluate pain and delirium and for early patient mobility.
   ii. Goals can be achieved using intermittent dosing administered routinely or as needed.
   iii. If unable to achieve goals with intermittent dosing, use a combination of bolus dosing with a continuous infusion.
      (a) In patients receiving a continuous infusion, use a bolus dose before or instead of increasing the infusion rate (a bolus dose has a faster onset and can eliminate the need for an increase in the infusion rate). An exception is with drugs such as propofol or dexmedetomidine, which can cause hypotension or bradycardia when bolused.
      (b) Use bolus dosing proactively (e.g., before dressing changes, suctioning, repositioning or other painful procedures).
   iv. Daily awakening involves an interruption of continuous infusion opioid or sedatives until the patient is awake (SAS score of at least 4 or RASS score of at least 0) or shows discomfort or pain necessitating reinitiation, ideally at a reduced dose. Although evidence is mixed, a scheduled daily interruption of continuous infusions is associated with several important benefits.
      (a) Assess the patient's neurologic function.
      (b) Reevaluate lowest effective opioid or sedative dose.
      (c) Prevent drug accumulation and overdose.
      (d) Reduce time on the ventilator (although one randomized study contradicts this by finding no reduction in the duration of mechanical ventilation or ICU stay with sedation interruption; JAMA 2012;308:1985-92).
      (e) Reduce mortality and ICU length of stay when combined with a spontaneous breathing trial.
      (f) Reduce symptoms of posttraumatic stress disorder and post-ICU syndrome.

B. Analgesics (Table 12)

Table 12. Intravenous Analgesics

	Fentanyl	Hydromorphone	Morphine
Pharmacokinetics			
Onset (min)	1–2	5–15	5–10
Duration of effect (hr)	1–5	2–6	2–4
Prolonged in renal failure	No	No	Yes
Prolonged in hepatic failure	Yes	Yes	Yes
Elimination half-life (hr)	2–4	2–3	3–4
Active metabolites	No	No	Yes
Adverse effects			
Hypotension	No	Yes	Yes
Flushing	No	Yes	Yes
Bronchospasm	No	No	Yes
Constipation	Yes	Yes	Yes

C. Sedatives
   1. Guidelines suggest using propofol or dexmedetomidine over benzodiazepines for sedation in mechanically ventilated adult patients. Benzodiazepines should be avoided when possible to prevent adverse outcomes, including prolonged duration of mechanical ventilation, increased ICU length of stay, and development of delirium (Table 13).
   2. Benzodiazepines
      a. Lorazepam
         i. Intermittent dosing 1–4 mg every 2–6 hours
         ii. Continuous infusion: Start at 1 mg/hour and titrate to goal (e.g., RASS, SAS). Total daily doses as low as 1 mg/kg can cause propylene glycol toxicity. If high-dose continuous infusion is used, monitor for an osmolal gap greater than 10–12 mOsm/L, indicating propylene glycol toxicity.
         iii. Lorazepam is the preferred benzodiazepine in severe hepatic dysfunction because of its metabolism with lack of active metabolites.
         iv. Continuous infusion lorazepam is generally used in mechanically ventilated patients. Generally, benzodiazepines infusions require mechanical ventilation because of potential for significant respiratory depression, even though there may be very niche reasons to use in non-intubated patients.
      b. Midazolam
         i. Intermittent dosing 1–4 mg every 15 minutes to 1 hour
         ii. Continuous infusion: Start at 1 mg/hour and titrate to goal (e.g., RASS, SAS).
         iii Often used for procedural sedation or daily dressing changes because of its rapid onset and short duration
         iv. Prolonged infusions of midazolam may accumulate because of its greater lipophilicity and active metabolites compared with lorazepam, especially in patients with renal dysfunction.
         v. Continuous infusion midazolam must only be used in mechanically ventilated patients.
      c. Diazepam
         i. Not routinely used as a sedative for mechanically ventilated patients because of accumulation of active metabolites with prolonged administration.
         ii. Often used for the treatment of alcohol withdrawal because of its rapid onset and long half-life.

Table 13. Intravenous Benzodiazepines

	Diazepam	Lorazepam	Midazolam
Pharmacokinetics			
Onset (minutes)	2–5	15–20	2–5
Duration of effect (hr)	2–4	4–6	1–2
Prolonged in renal failure	Yes	No	Yes
Prolonged in hepatic failure	Yes	No	Yes
Elimination half-life (hr)	24–120	10–20	1–10
Active metabolite	Yes	No	Yes
CYP3A4 interactions	Yes	No	Yes
Adverse effects			
Hypotension	Yes	No	No
Thrombophlebitis	Yes	Maybe	No
Propylene glycol toxicity	No	Yes	No

CYP = cytochrome P450.

3. Propofol
    a. Rapid onset (1–2 minutes) and short duration (3–5 minutes or longer if prolonged infusion)
    b. Initiate at 5 mcg/kg/minute and titrate to achieve sedation goals by 5 mcg/kg/minute every 5 minutes. Avoid prolonged infusions, typically greater than 48 hours, at greater than 80 mcg/kg/minute because of the patient's risk of developing propofol-related infusion syndrome.
    c. Avoid loading or bolus doses because of the risk of hypotension.
    d. Continuous infusion recommended to be used only in intubated patients because of the risk of respiratory depression. Propofol may also be used for procedural sedation, where smaller intermittent bolus doses would be given, without requiring mechanical ventilation.
    e. Propofol has no significant analgesic activity. If a patient has pain, propofol must be combined with an analgesic.
    f. Monitoring
        i. Blood pressure
        ii. Triglyceride concentrations should be obtained when propofol is administered for longer than 48 hours or at a rate of at least 50 mcg/kg/minute. An alternative agent should be given if severe hypertriglyceridemia occurs because the patient's risk of developing pancreatitis increases. An exact threshold is uncertain, but clinicians often consider an alternative when serum triglyceride concentrations exceed 500–800 mg/dL.
        iii. Calories provided from 10% lipid emulsion (1.1 kcal/mL). May need to adjust lipid or calories provided by nutrition support (i.e., EN or PN)
        iv. Propofol-related infusion syndrome is more likely to occur with infusion rates of at least 80 mcg/kg/minute for at least 48 hours, and is associated with metabolic acidosis, cardiac failure, arrhythmias (e.g., bradycardia), cardiac arrest, rhabdomyolysis, hyperkalemia, and kidney failure.
    g. Propofol is more commonly used than benzodiazepines because of its shorter duration, easy titration, predictability, and less risk of delirium.
4. Dexmedetomidine
    a. Sedative properties through central and peripheral α_2-receptor agonist activity
    b. Extent of analgesic activity in patients in the ICU is not well described.
    c. Does not cause respiratory depression and therefore can be safely used in nonintubated patients.
    d. Rapid onset (5–15 minutes if bolus, longer without bolus) and short duration (2-hour half-life). Longer duration in patients with severe hepatic dysfunction
    e. A loading dose is suggested for patients undergoing surgery; however, loading doses are not recommended for patients in the ICU because of the risk of bradycardia and hypotension.
    f. Maintenance dose of 0.2–0.7 mcg/kg/hour is approved by the U.S. Food and Drug Administration for a maximum of 24 hours; however, there is evidence showing the safety and efficacy of prolonged infusions at doses of up to 1.5 mcg/kg/hour, and this is most commonly used in practice.
    g. Compared with benzodiazepines, dexmedetomidine is associated with a lower prevalence of ICU delirium in some studies (Intensive Care Med 2021;47:943-60).
    h. Results from the MIDEX and PRODEX studies show that dexmedetomidine is noninferior to midazolam and propofol in maintaining light to moderate sedation. Dexmedetomidine reduced the duration of mechanical ventilation compared with midazolam but was noninferior compared to propofol (JAMA 2012;307:1151-60).
    i. The SPICE III trial was a multicenter, open-label, randomized trial examining early use (within 12 hours of intubation) of dexmedetomidine to usual care continuous sedation targeting light sedation (RASS goal of +1 to –2). No significant difference was observed in 90-day all-cause mortality rates between groups; however, mean RASS scores were –4 at baseline and deeper sedation (RASS –2 to +1) was permitted despite targeting light sedation (N Engl J Med 2019;380:2506-17).

j. A recent multicenter study (N Eng J Med 2021;384:1424-36) compared sedation with dexmedetomidine and propofol in mechanically ventilated adults with sepsis. There was no difference in number of days alive without delirium or coma, and no difference in ventilator free days at 28 days or 90-day mortality. It is still unclear if sedative choice has an impact on clinical outcomes.
k. Monitoring: Primary adverse effects are dose-related bradycardia and hypotension.
l. Does not cause drug dependency, but withdrawal symptoms (e.g., nausea, vomiting, agitation, hypertension) have occurred after prolonged use (1 week). Additionally, oral clonidine can be used to assist with weaning from decmedetomidine because of similar alpha-2 agonist activity.
m. Dexmedetomidine can be used as an adjunct in ethanol withdrawal, but not as replacement for benzodiazepine use.

5. Ketamine
   a. *N*-methyl-D-aspartate receptor antagonist
   b. Has both analgesic and sedative properties
   c. Does not cause respiratory depression; however, does cause bronchodilation, which is beneficial in patients with asthma or chronic obstructive pulmonary disease
   d. Dosing and titration strategies vary widely by institution.
   e. Minimal effect on bowel motility
   f. Risk of emergence delirium when high doses are tapered off. It is unclear whether benzodiazepines will reduce the risk of emergence.
   g. Major adverse effects include hypertension, tachycardia, and delirium.
   h. Has been associated with an opioid-sparing effect, especially in patients with chronic pain
   i. Guidelines suggest using low-dose ketamine as an adjunct to opioid therapy when seeking to reduce opioid use in postsurgical patients. There is no routine role for ketamine in sedation or in prevention and treatment of delirium.

D. Assessment and management of delirium
   1. Delirium is an acute change in cognitive function characterized by disorganized thought, altered level of consciousness, and inattentiveness.
   2. Delirium is associated with increased mortality, prolonged length of stay in the ICU, and cognitive impairment after ICU discharge.
   3. Validated tools to proactively identify and assess delirium include the Confusion Assessment Method for the ICU (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC). The CAM-ICU is designed to detect delirium at the time of testing, whereas the ICDSC detects delirium during a nursing shift. For a detailed description of delirium monitoring tools, see www.icudelirium.org/medical-professionals/delirium/monitoring-delirium-in-the-icu.
   4. Nonpharmacologic interventions are preferred to pharmacologic treatment. These interventions include maintaining communication with the patient, reorienting the patient (to person, place, and time), maximizing uninterrupted sleep (e.g., control light and noise, cluster patient care activities, decrease stimuli at night), providing access to natural lighting (rooms with windows), removing unnecessary equipment from room, correcting sensory deficits (e.g., hearing aids, glasses), removing unneeded invasive devices (e.g., urinary catheters, intravenous lines, endotracheal tubes, enteral feeding tubes), minimizing physical restraint, and encouraging patient autonomy and early mobility.
   5. Correctable causes of delirium include hypotension, hypoxia, infection, and electrolyte disturbances.
   6. Few interventions have been shown to improve delirium-related outcomes; therefore, a strong focus should be put on minimizing or treating reversible risk factors such as avoiding or minimizing the dose of benzodiazepines and other medications that can cause delirium (e.g., opioids, anticholinergic medications).

7. Guidelines discourage routine use of antipsychotics for the treatment of delirium. However, they should be considered when patients experience significant distress because of symptoms of delirium. Antipsychotics should be used as a short treatment until symptoms resolve and use reassessed at transitions of care.

E. Pharmacologic treatment of delirium (Table 14)
   1. Haloperidol
      a. Although commonly used, there is no evidence that haloperidol reduces the duration of delirium.
      b. Monitoring
         i. Hypotension
         ii. Assess QTc interval at baseline and routinely during haloperidol administration. In addition, monitor for other drugs that could prolong QTc interval. Prolongations of greater than 500 milliseconds are associated with a higher risk of torsades de pointes.
         iii. Extrapyramidal effects, including laryngeal dystonia and dysphagia, are more common with chronic oral administration than with intravenous administration.
      c. Lower initial doses of haloperidol (1–2.5 mg) should be used in older adults because of greater risks of adverse effects, including QTc prolongation.
      d. Doses of haloperidol for acute agitation can be doubled every 20 minutes until an effective dose is reached.
   2. Atypical antipsychotics
      a. Atypical or second-generation antipsychotics can reduce the duration of delirium in critically ill patients.
      b. Atypical antipsychotics are associated with a lower incidence of extrapyramidal symptoms (EPSs) than is haloperidol.
      c. Differences between agents are half-life, the risk of QTc prolongation, sedation, incidence of metabolic syndrome, and risk of EPSs.
         i. Sedative effects may be beneficial (e.g., hyperactive vs. hypoactive delirium).
         ii. Agents with a shorter half-life (quetiapine) generally act faster and can be quickly titrated.
         iii. Olanzapine and risperidone have less risk of QTc prolongation but should still be monitored.

Table 14. Medications Used to Treat Delirium

Medication	Initial Dosing	Dosage Forms	Half-life (hr)	Adverse Effects
Haloperidol	2.5 mg every 6 hr	Tablet, IM, IV	18	QTc prolongation EPSs
Quetiapine	25 mg twice daily	Tablet	6	Sedation QTc prolongation
Olanzapine	5 mg daily	Tablet, ODT, IM	33	Sedation QTc prolongation (less than other agents)
Risperidone	0.5 mg twice daily	Tablet, ODT, solution, IM[a]	24	EPS (doses > 6 mg/day) QTc prolongation (less than other agents)
Ziprasidone	20 mg twice daily	Capsule, IM	7	Sedation QTc prolongation

[a]IM formulation of risperidone is a long-acting formulation that is not indicated for acute delirium management.
EPS = extrapyramidal symptom; IM = intramuscular(ly); IV = intravenous(ly); ODT = orally disintegrating tablet.

F. Neuromuscular blockade in patients in the ICU (Table 15)

1. Neuromuscular blockade is typically indicated for intubated patients with severe respiratory failure (e.g., ARDS, status asthmaticus) despite optimization of analgesia, sedation, and ventilator management.
2. In patients with severe ARDS (defined as a Pao_2/FiO_2 ratio less than 150), a 48-hour infusion of cisatracurium (15-mg bolus followed by 37.5 mg/hour for 48 hours) showed a decreased adjusted 90-day mortality (N Engl J Med 2010;363:1107-16). More recent data analyses using a similar regimen had conflicting results with no difference in mortality or ICU-related weakness, but increased adverse cardiovascular events (N Engl J Med 2019;380:1997-2008). Notable differences between these studies (e.g., the degree of sedation in the control group and differences in use of prone positioning) may have contributed to the discrepancy. Of note, in these studies, the cisatracurium infusion was a fixed dose and was not adjusted on the basis of the monitoring parameters described later (e.g., train-of-four [TOF]). Because of the lack of a clear benefit in ARDS, neuromuscular blockers should be reserved for patients who are persistently hypoxemic or at risk for ventilator injury despite deep sedation. Neuromuscular blockers should be avoided in patients who tolerate ventilation using lighter sedation.
3. Neuromuscular blockers are also used as adjunctive agents to control severe intracranial hypertension in patients with neurologic injury (e.g., traumatic brain injury).
4. Neuromuscular blockers are typically used once efforts to facilitate ventilation have failed (e.g., poor oxygenation, dyssynchrony, high intrathoracic pressures that put the patient at risk for barotrauma) and a combination of high-dose opioids and sedatives have failed (i.e., patient continues to have poor oxygenation).
5. Neuromuscular blockers may be used to attenuate shivering during therapeutic hypothermia.
6. Never use neuromuscular blockers in a patient who is not completely sedated or does not have adequate pain control.
7. Neuromuscular blockers should be used only in conjunction with a continuously infused sedative following appropriate pain control. Sedatives should have amnestic properties (e.g., benzodiazepines, propofol). Analgesics can continue to be used and optimized as needed. Dexmedetomidine does not provide the depth of sedation required for neuromuscular blocker infusion. Many practitioners insist on the combination of a sedative and an analgesic in paralyzed patients.

Table 15. Neuromuscular Blocking Agents

Recommendation	Pancuronium[a]	Vecuronium	Rocuronium	Atracurium	Cisatracurium
Duration of effect (hr)	0.75–1.5	0.5–0.75	0.3–1	0.25–0.5	0.5–1
Prolonged in renal failure	Yes	Yes	Yes	No	No
Prolonged in hepatic failure	Yes	Yes	Yes	No	No
Loading dose	0.08 mg/kg	0.1 mg/kg	0.6–1 mg/kg	0.4 mg/kg	0.1 mg/kg
Maintenance dose	0.8-1.7 mcg/kg/min	0.8-1.7 mcg/kg/min	3–8 mcg/kg/min	4-20 mcg/kg/min	2–10 mcg/kg/min
Adverse effects					
Tachycardia	Yes	No	Yes	No	No
Hypotension	No	No	No	Dose-dependent	No

[a]No longer commercially available on the market

8. Concerns with neuromuscular blockade
   a. Can mask seizure activity
   b. Prolonged use is associated with critical illness poly-neuromyopathy, which is characterized by prolonged muscle weakness, especially with steroid based neuromuscular blocking agents.

c. Can mask insufficient analgesia and sedation
d. Increased risk of venous thromboembolism (VTE)
e. Increased risk of skin breakdown and decubitus
f. Corneal abrasions caused by eye dryness and lack of blinking; prevent by applying ophthalmic ointment or drops to eyes every 6–8 hours

9. Monitoring
   a. Neuromuscular blockers must be monitored to prevent an excessive degree of blockade and prolonged paralysis.
   b. The goal of neuromuscular blockade is to facilitate safe and optimal mechanical ventilation strategies using the minimal degree of neuromuscular blockade needed.
   c. Even with appropriate individualized dosing and monitoring of neuromuscular blockade, a principal adverse effect is prolonged muscle weakness after discontinuation. This can dramatically slow patient recovery, increasing the need for health care resources (e.g., physical therapy, rehabilitation). For this reason, it must be emphasized that the need for therapeutic paralysis must be carefully considered and reevaluated every day.
   d. A simple way to assess the appropriateness of the paralytic is as follows. Regularly (e.g., once daily) temporarily discontinue the drug to determine the time needed for the patient to move or breathe spontaneously. Although not applicable to all patients, this "drug holiday" can be useful for the following reasons:
      i. Assess sedation and adjust sedatives as needed (e.g., if the patient is agitated after the drug is discontinued, he or she is not receiving adequate sedation or analgesia).
      ii. Assess the need for continued blockade (e.g., if the patient can maintain oxygenation, then perhaps the drug is no longer necessary).
      iii. Assess the dose of the paralytic (e.g., determine whether the paralysis wore off within the expected time according to the expected drug duration); this is especially important for drugs such as vecuronium because of the long half-life and dependence on end organ clearance.
      iv. Note that the studies listed earlier (N Engl J Med 2010;363:1107-16; N Engl J Med 2019;380:1997-2008) used cisatracurium continuously (without a holiday) for 48 hours without an increased incidence of prolonged weakness.
   e. A peripheral nerve stimulator can be used in conjunction with drug holidays to assess the level of neuromuscular blockade and guide drug dosing.
      i. The TOF refers to peripheral nerve stimulation using four electrical impulses, usually applied to the ulnar (preferable) or facial nerves.
      ii. Obtain a baseline TOF before initiation to determine patient sensitivity to impulses. At baseline, patients without existing neuromuscular impairment should have 4/4 twitches (1 twitch per impulse).
      iii. During neuromuscular blockade infusions for respiratory failure, patients should typically be maintained at one or two twitches, which indicates 85%-90% receptor blockade. Zero out of four twitches indicates complete paralysis, with 100% receptor blockade, and is clinically undesirable.
      iv. Technical problems that limit the accuracy of TOF monitoring include the presence of perspiration or tissue edema. The TOF monitor may no longer be accurate if the electrodes are moved after the neuromuscular blocker is initiated.
10. In addition to the monitoring described, clinical assessment involves adjusting the neuromuscular blocker dose to prevent patient-ventilator dyssynchrony (e.g., "bucking" the ventilator, elevated peak airway pressures).

11. Avoid other medications or electrolyte abnormalities that can potentiate or inhibit paralysis (Table 16).

Table 16. Interactions with Neuromuscular Blockers

	Potentiate Blockade	Antagonize Blockade
Drugs	Corticosteroids Aminoglycosides Clindamycin Tetracyclines Polymyxins Calcium channel blockers Type Ia antiarrhythmics Furosemide Lithium	Aminophylline Theophylline Carbamazepine Phenytoin (chronic)
Electrolyte disorders	Hypermagnesemia Hypocalcemia Hypokalemia	Hypercalcemia Hyperkalemia

Patient Cases

8. An older woman is admitted to the ICU for acute decompensated heart failure and acute kidney injury with an ejection fraction of less than 30%. She is administered a continuous infusion of bumetanide; however, the benefit is limited because of her acute-on-chronic kidney disease. She is intubated on ICU day 2 because of worsening pulmonary edema and hypoxia. After intubation, her RASS score is 0, her CAM-ICU is negative, and her CPOT score is 4. Her blood pressure is 120/70 mm Hg and heart rate is 88 beats/minute. Which is the best recommendation for achieving her analgesia, sedation, and delirium goals?
    A. Initiate morphine at 5 mg/hour and titrate as needed.
    B. Administer haloperidol 5 mg intravenously as needed.
    C. Administer fentanyl 25 mcg intravenously every hour as needed.
    D. Initiate lorazepam 2 mg/hour and titrate as needed.

Questions 9–11 pertain to the following case.

A 42-year-old woman with ARDS and a significant history of alcohol and tobacco abuse is transferred to the medical ICU from an outside hospital. She presented to the outside hospital after 1 week of productive cough, fever, chills, and increased shortness of breath. On admission to the medical ICU, she is hypotensive (80/60 mm Hg), tachycardic (130 beats/minute), and febrile (body temperature 102.2°F [39.0°C]). Her ABG shows pH 7.1, $Paco_2$ 56 mm Hg, Pao_2 49 mm Hg, HCO_3- 16 mEq/L, and Sao_2 76% on 100% FiO_2. The only other significant laboratory results are SCr 2.1 mg/dL and WBC 16×10^3 cells/mm^3. She is achieving her sedation goals with continuous infusions of propofol 20 mcg/kg/minute and fentanyl 200 mcg/hour.

9. After several nonpharmacologic attempts to improve her oxygenation fail, she is paralyzed, and her ventilator settings are adjusted accordingly. Which statement about neuromuscular blockade in this patient is most appropriate?
    A. Opioids should be discontinued to avoid prolonged neuromuscular weakness.
    B. Vecuronium is the agent of choice.
    C. Sedatives should be titrated to maintain a RASS goal of 0 to –2 during neuromuscular blockade.
    D. Neuromuscular blockers should be titrated to the minimal dose necessary to achieve ventilator synchrony.

Patient Cases *(Cont'd)*

10. The patient was initiated on neuromuscular blockade as instructed and synchronous with the ventilator, but about 8 hours later, she began to move around violently in her bed. At this time, she was tachycardic (heart rate 120 beats/minute) and appeared agitated; her Sao_2 dropped to 80%. Which action is best?
    A. Double the rate of the neuromuscular blocker every 5 minutes as needed until the patient stops moving.
    B. Increase the propofol infusion rate as needed to achieve sedation goals.
    C. Initiate a dexmedetomidine infusion.
    D. Check the TOF.

11. After that event, the patient did poorly the rest of the night. The patient was initiated on a norepinephrine infusion at 0.02 mcg/kg/minute to maintain an adequate blood pressure. Other medications initiated overnight included piperacillin/tazobactam, vancomycin, and gentamicin. By morning, her SCr has increased to 2.8 mg/dL, and the night shift nurse reports that the patient has had 0/4 twitches on TOF for the past 8 hours. Pertinent electrolyte values include K^+ 4.9 mEq/L, calcium 9 mg/dL, and magnesium 2 mg/dL. What is most likely to potentiate the effects of the neuromuscular blocker?
    A. Piperacillin/tazobactam.
    B. Gentamicin.
    C. Norepinephrine.
    D. Potassium concentration.

VII. GLUCOSE CONTROL

A. History of blood glucose control
    1. 2001: Study by van den Berghe et al. of surgical ICU patients showed a significant morbidity and mortality benefit of maintaining blood glucose at 80–110 mg/dL, despite the increased risk of hypoglycemia at 5.1% versus 0.8%.
    2. 2006: Study by van den Berghe et al. of primarily medical ICU patients showed no mortality benefit associated with maintaining blood glucose in the range of 80–110 mg/dL in the entire study population. The study showed a reduction in ventilator time, length of stay, and mortality in patients with an ICU length of stay of 3 days or more. The incidence of hypoglycemia (18%) was higher than previously reported.
    3. Subsequent investigations of tight glycemic control (80–110 mg/dL) never replicated the mortality benefit seen in the 2001 study. Studies showed much higher rates of hypoglycemia with tight glycemic control.
    4. 2009: Results of a large, international, randomized study (NICE-SUGAR) involving more than 6000 critically ill medical and surgical patients showed higher mortality and higher risk of hypoglycemia in patients receiving intensive blood glucose control (goal glucose 81–108 mg/dL) compared with patients having a goal of 180 mg/dL or less (mean blood glucose 142 mg/dL).
    5. The 2024 Society of Critical Care Medicine guidelines for using an insulin infusion to manage hyperglycemia in general critically ill patients suggest using a blood glucose of 180 mg/dL or higher as a trigger for insulin therapy, adjusted to keep blood glucose between 140 and 200 mg/dL using an insulin protocol that achieves a low rate of hypoglycemia (blood glucose 70 mg/dL or less).
    6. The 2021 SSC guidelines recommend a protocolized approach to insulin therapy, initiating insulin therapy at a glucose level greater than 180 mg/dL. A typical target blood glucose concentration range is 144–180 mg/dL for patients with sepsis.

B. Treatment strategies to achieve glycemic control in critically ill patients
   1. For a continuous insulin infusion approach, use a validated dosing protocol that considers blood glucose concentration, rate of change, and insulin infusion rate.
   2. Intravenous insulin is preferred for patients with type 1 diabetes, patients with hyperglycemia who are hemodynamically unstable, and patients in whom long-acting basal insulin should not be initiated because of changing clinical status. Once patients are in stable condition, they can be considered for transitioning to a protocol-driven subcutaneous insulin regimen.
   3. Regularly scheduled subcutaneous administration of basal or rapid-acting insulin can prevent hyperglycemia in clinically stable patients who do not need an intravenous infusion of insulin. The use of subcutaneous insulin is not recommended in patients receiving vasopressors, patients with significant peripheral edema, or patients for whom rapid correction of blood glucose is warranted.
   4. Subcutaneous sliding-scale or correction factor insulin should not be the sole method of glucose control in critically ill patients. A sliding-scale or correction factor insulin regimen can be used in conjunction with the regularly scheduled subcutaneous doses; however, the baseline of insulin administered should be adjusted daily to prevent hyperglycemia and the need for additional doses of insulin.

C. Monitoring blood glucose
   1. For a continuous insulin infusion approach, monitoring of blood glucose every 1–2 hours is typically needed to provide safe and effective therapy.
   2. Interpret point-of-care testing of capillary blood with caution because it can overestimate plasma glucose values. Overestimation of blood glucose is more common in patients with anemia, hypotension, or hypoperfusion. It is also more common when blood glucose is in the hypoglycemic or hyperglycemic range.
   3. Arterial or venous whole blood sampling is recommended instead of fingerstick capillary blood glucose testing in patients with shock or severe peripheral edema and for patients on a prolonged insulin infusion.

VIII. PREVENTING STRESS ULCERS

A. Mucosal bleeding in critically ill adults
   1. The incidence of stress-related mucosal bleeding in critically ill adults is estimated to be 2.5%.
   2. Signs and symptoms of stress ulcers include hematemesis, gross blood in gastric tube aspirates, coffee ground emesis or aspiration from gastric tube, and melena. Clinically significant stress ulcers are defined as those that cause hemodynamic compromise or necessitate blood transfusion.

B. Prophylactic therapy for stress ulcers
   1. Prophylactic medications are recommended for any one of the following major risk factors:
      a. Respiratory failure necessitating mechanical ventilation (for more than 48 hours)
      b. Coagulopathy, defined as platelet count less than 50,000 cells/mm^3, INR greater than 1.5, or activated partial thromboplastin time greater than twofold the control value. (Note: Prophylactic or treatment doses of anticoagulants do not constitute coagulopathy.)
   2. Prophylactic medications or continuing home acid suppressive regimens are also recommended for any patient with a history of gastrointestinal (GI) ulceration or bleeding within 1 year before ICU admission.
   3. Prophylactic medications are recommended for patients with two or more of the following risk factors (although data on this approach are lacking):
      a. Head or spinal cord injury
      b. Severe burn (more than 35% of body surface area)
      c. Hypoperfusion
      d. Acute organ dysfunction

e. High doses of corticosteroids (more than 250 mg/day of hydrocortisone or equivalent)
f. Liver failure with associated coagulopathy
g. Transplantation
h. Acute kidney injury
i. Major surgery
j. Multiple trauma

C. Strategies for stress ulcer prophylaxis (SUP) (see Table 17 for specific medications)
1. Efficacy of intravenous histamine-2 (H_2)-blockers in preventing stress-related upper GI bleeding has been shown in several clinical trials. These are commonly administered enterally when possible because of excellent bioavailability; however, evidence of efficacy is primarily with the intravenous administration of H_2-blockers.
2. Proton pump inhibitors (PPIs) also prevent stress-related mucosal bleeding and are commonly administered enterally, when possible, given their excellent bioavailability.
3. Recent data analyses assessing PPIs versus placebo found no difference in mortality or clinically important events, which were a composite of clinically important GI bleeding, pneumonia, *C. difficile* infection, or myocardial ischemia. However, of note are the limited therapy duration (median of 4 days) and higher rate of GI bleeding in the placebo group (4.2% vs. 2.5%). Another large study comparing PPIs with H_2-blockers found no difference in mortality, but a lower incidence of clinically important GI bleeds with PPIs (1.3% vs. 1.8%; RR 0.73 [95% CI, 0.52–0.92]). However, 20.1% of patients randomized to H_2-blockers received PPIs, making it difficult to draw definitive conclusions and apply them to clinical practice (JAMA 2020;323:616-26).
4. A recent meta-analysis compared the efficacy and safety of H_2-blockers, PPIs, and sucralfate against each other or placebo. H_2-blockers and PPIs had a significant reduction in clinically important GI bleeding in high risk critically ill patients (Intensive Care Med 2018;44:1-11). No differences were found in mortality or infections. There was no benefit found with sucralfate in any endpoint. Although this meta-analysis has limitations of heterogeneous patient populations, definitions, and endpoints, it supports the use of H_2-blockers or PPIs in patients with a high risk of bleeding.
5. Regardless of the drug choice or route, it is important to discontinue therapy when risk factors are no longer present to avoid unnecessary drug interactions, adverse effects (e.g., pneumonia), and increased costs. This step is easily overlooked, with the result that patients are discharged from hospitals and then continue to take acid-suppressive therapy with no indication.
6. Recent studies suggest enteral nutrition may have protective effects against GI bleeding. Pharmacologic prophylaxis may not provide additional benefit to EN, but may increase risk for adverse effects such as pneumonia. Additional studies are needed to confirm these outcomes.
7. Not recommended for prevention
   a. Antacids.
   b. Sucralfate is inferior to H_2-blockers and is therefore not recommended for preventing stress ulcers. In addition, it can cause obstruction of enteral feeding tubes and aluminum toxicity in patients with renal failure.
8. Safety: The benefits of preventing stress ulcers by increasing the stomach pH must be weighed against an increased risk of infection, including *C. difficile,* hospital-acquired pneumonia, and community-acquired pneumonia (for patients discharged with a PPI).

Table 17. Medications for Stress Ulcer Prophylaxis

Class	Examples and Dosing	Adverse Effects	Notes
H_2-receptor blockers	Famotidine 20 mg IV or PO every 12 hr Nizatidine 150 mg PO every 12 hr Cimetidine 300 mg PO every 6 hr	Mental status changes, thrombocytopenia	Excellent bioavailability Low cost Potential for reduced efficacy over time (tachyphylaxis) Dose adjustment for renal dysfunction Low risk of nosocomial pneumonia Cimetidine not routinely used because of drug interactions (strong P450 inhibitor) and adverse effects
Proton pump inhibitors	Omeprazole 20 mg PO daily Powder for oral suspension available Esomeprazole 20–40 mg PO or IV daily Lansoprazole 30 mg PO or IV daily Delayed-release orally disintegrating tablets and oral suspension available Pantoprazole 40 mg PO or IV daily granules available for oral or tube administration	Headache, diarrhea, constipation, abdominal pain, nausea	Solutions of certain PPIs may be compounded; refer to individual package inserts for instructions No adjustment needed for renal or liver dysfunction Higher cost than H_2-blockers Administration problems may occur when given by feeding tubes Risk of ventilator-associated pneumonia increased Risk of *C. difficile* infection (nosocomial or community acquired)

H_2 = histamine-2; IV = intravenous; PO = orally; PPI = proton pump inhibitor.

Patient Case

Questions 12 and 13 pertain to the following case.

A 73-year-old woman (weight 84 kg) is admitted to the ICU after a pneumonectomy and has been intubated for 4 days. Her blood pressure is 104/65 mm Hg, heart rate is 88 beats/minute, and Sao_2 values are 98% on 40% FiO_2 and positive end-expiratory pressure 5 cm H_2O; her Glasgow Coma Scale score is 11. Her other laboratory values are normal. Her medications include simvastatin 20 mg every night, aspirin 81 mg/ day, metoprolol 25 mg twice daily, heparin 5000 units subcutaneously every 8 hours, and 0.9% sodium chloride intravenously at 75 mL/hour.

12. The surgeon would like to initiate SUP. Which is the best recommendation for this patient?
    A. Administer famotidine 20 mg per tube every 12 hours.
    B. Administer magnesium hydroxide 30 mL per tube four times daily.
    C. Administer sucralfate 1 g per tube four times daily.
    D. SUP is not indicated.

13. One week later, the patient is extubated but still in the ICU. Her Glasgow Coma Scale score is 15, blood pressure is 112/70 mm Hg, and heart rate is 75 beats/minute, but her appetite is poor. Which statement is most appropriate regarding SUP for this patient?
    A. SUP should continue until the patient is discharged from the ICU.
    B. SUP should be discontinued now.
    C. Continue SUP until patient is eating.
    D. SUP should be discontinued at hospital discharge.

IX. PHARMACOLOGIC THERAPY FOR PREVENTING VENOUS THROMBOEMBOLISM

A. General overview: VTE is a common complication of critical illness, with an incidence of deep vein thrombosis of 8%–40% and pulmonary embolism of up to 12%.

B. Risk factors for VTE
    1. Critically ill patients are usually at high risk of VTE.
    2. Additional risk factors include surgery, major trauma, lower extremity injury, immobility, malignancy, sepsis, heart failure, respiratory failure, venous compression, previous VTE, increasing age, pregnancy, erythropoiesis-stimulating agents, obesity, and central venous catheterization.

C. Recommendations for critically ill patients
    1. American Society of Hematology guidelines
        a. Recommends low-molecular-weight heparin (LMWH) or low-dose unfractionated heparin (UFH) over no prophylaxis or mechanical prophylaxis. Guidelines also suggest using LMWH over UFH. LMWH compared with UFH appeared to have a moderate impact on mortality and VTE, with a decreased incidence of heparin-induced thrombocytopenia (HIT).
        b. Nonpharmacologic prevention
            i. Early mobility is the ideal nonpharmacologic therapy, though the definition of mobility varies.
            ii. Mechanical prophylaxis with intermittent pneumatic compression or graduated compression stockings is recommended for medical patients at risk of VTE who have a contraindication to pharmacologic anticoagulation (e.g., thrombocytopenia, severe coagulopathy, active bleeding, recent intracerebral hemorrhage).

c. Suggests pharmacologic or mechanical VTE prophylaxis alone over mechanical combined with pharmacologic prophylaxis. This is because of the potential increased risk of complications with combination therapy without any perceived benefit. For surgical patients, combined mechanical and pharmacologic prophylaxis is suggested over pharmacologic prophylaxis alone.
d. The guidelines provide separate postoperative recommendations. A detailed assessment is beyond the scope of this text, and readers are encouraged to see the guidelines cited in the References list for more information.

2. SSC recommends pharmacologic VTE prophylaxis with LMWH over unfractionated heparin unless a contraindication to therapy exists.

D. Pharmacologic prophylaxis (see Table 18 for dosage)
1. Unfractionated heparin
a. Low cost
b. Twice- versus three-times daily administration: Two meta-analyses have been completed on the subject. The first, in 2007, concluded that there was no difference in efficacy, but three-times daily administration was associated with a slightly higher risk of bleeding. The second, in 2011, found no difference in efficacy or safety with either regimen.
c. Risk of HIT lower than that of full anticoagulation doses
2. LMWHs
a. All considered therapeutically equivalent
b. Dalteparin is renally eliminated but can be considered in patients with creatinine clearance (CrCl) less than 30 mL/minute/1.73 m^2 because of its low accumulation.
c. Low risk of HIT
d. In the largest trial of VTE prevention in critical care patients, dalteparin 5000 units subcutaneously once daily provided better protection against pulmonary embolism, similar protection against proximal deep venous thrombosis with no difference in bleeding, and less HIT than unfractionated heparin 5000 units twice daily.
3. Fondaparinux
a. Can be safe in patients with a history of HIT
b. Data on reversal of fondaparinux are lacking
c. Contraindicated for CrCl less than 30 mL/minute/1.73 m^2
d. Limited data in critically ill patients
4. Direct oral anticoagulants
a. Rivaroxaban was evaluated against enoxaparin in a study of acutely ill medical patients needing hospitalization. Although rivaroxaban was as efficacious as enoxaparin at study day 10, there was an excess risk of bleeding in the rivaroxaban group. Patients with cardiogenic or septic shock with the need for vasopressors were excluded. Rivaroxaban is renally eliminated and is not recommended in patients with significant renal insufficiency.
b. Apixaban was evaluated against enoxaparin in a study of acutely ill medical patients needing hospitalization. There was no difference in rates of VTE, but a higher bleeding rate with apixaban. Patients with septic shock were also excluded from this trial.
c. Compared with heparins, there is less experience in reversal of Factor Xa inhibitors in clinical practice.
d. Rivaroxaban is the only direct oral anticoagulant (DOAC) FDA-approved for VTE prophylaxis in medically ill patients. However, the safety and efficacy in critically ill patients is still unclear.

E. Special populations
   1. Impaired kidney function
      a. If estimated CrCl is less than 30 mL/minute/1.73 m^2, LMWH dose reduction is usually necessary. If CrCl is less than 20 mL/minute/1.73 m^2 or the patient requires dialysis, dosing information is limited for LMWH; anti-Xa monitoring might not be reliable in patients undergoing dialysis.
      b. Alternatively, if estimated CrCl is less than 30 mL/minute/1.73 m^2, dalteparin can be used because it has minimal renal metabolism.
      c. Fondaparinux is contraindicated in patients with an estimated CrCl less than 30 mL/minute 1.73 m^2.
      d. Low-dose unfractionated heparin is minimally renally eliminated and is safe to use in patients with reduced kidney function.
   2. Overweight or underweight adults: For patients with obesity, some experts recommend increasing unfractionated heparin dose to 7500 units and LMWH prophylaxis doses by 30%–100% if body mass index (BMI) is greater than 40 kg/m^2; a peak (4 hours postdose) anti-Xa of 0.2–0.4 IU/mL is recommended. Note that these recommendations have not been validated in controlled trials and are considered expert opinion only (see Ann Pharmacother 2009;43:1064-83).
   3. Patients admitted with major traumatic injuries: Enoxaparin 30 mg every 12 hours is more effective than other regimens. Early initiation of pharmacologic prophylaxis (within 48 hr) in stable trauma patients was associated with lower incidence of VTE and no increased risk for bleeding complications or mortality (J Trauma Acute Care Surg 2021;90:54-63).

F. Antithrombotic therapy and regional anesthesia
   1. Critically ill patients often have their spinal meninges accessed for either therapeutic (epidural anesthesia, lumbar drains) or diagnostic (lumbar puncture) purposes.
   2. The combination of antithrombotic medications with these techniques is associated with an elevated risk of spinal or epidural hematoma, which can lead to ischemia and paralysis. The risk is impacted by the dose, timing, and quantity of antithrombotic medications in relation to needle placement or catheter removal.
   3. The American Society of Regional Anesthesia and Pain Medicine published guidelines on regional anesthesia in patients receiving antithrombotic or thrombolytic therapy. Pertinent details regarding VTE prophylaxis are listed below. For a comprehensive description of recommendations, refer to the guidelines (Reg Anesth Pain Med 2018;43:263-309).
      a. Subcutaneous unfractionated heparin (e.g., 5000 units every 8–12 hr) should be held 4–6 hours before needle placement or catheter removal, and the subsequent dose may be administered after at least 1 hour. Higher doses (e.g., at least 20,000 units/day) should be held for a longer interval.
      b. Prophylactic LMWH (e.g., enoxaparin 40 mg daily and 30 mg every 12 hr) should be held at least 12 hours before needle placement or catheter removal. Epidural catheters can be maintained with once daily dosing without other medications that impact hemostasis. In twice daily dosing, however, catheters may not be maintained. The subsequent dose may be administered at least 4 hours after catheter removal. Extra caution and consideration must be taken in patients with renal disease.
         i. The first dose of LMWH should be at least 2 hours after catheter removal.
         ii. Catheter removal should be at least 10–12 hours after the last LMWH dose (longer in patients with renal disease).
      c. Because of a lack of data, the use of fondaparinux should be avoided.
      d. Because of various DOAC regimens with differences in half-life and elimination, check for specific recommendations regarding regional analgesia.

G. Prevention of VTE: Pharmacologic options in critically ill patients (see Table 18)

Table 18. Prevention of Venous Thromboembolism: Pharmacologic Options

Medication	Mechanism	Dosing[a]	Adjustment for Renal Dysfunction
Unfractionated heparin	Factor Xa and indirect thrombin inhibition	5000 units SC two or three times daily	None
Low-molecular-weight heparin	Factor Xa inhibition and some indirect thrombin inhibition	Enoxaparin 40 mg SC daily Dalteparin 5000 units SC daily	CrCl < 30 mL/min/1.73 m^2: enoxaparin 30 mg SC daily
Fondaparinux	Factor Xa inhibition	2.5 mg SC daily	Contraindicated for CrCl < 30 mL/min/1.73 m^2

[a]Patients within normal body mass index (BMI) range.
SC = subcutaneously.

X. PREVENTING VENTILATOR-ASSOCIATED PNEUMONIA

A. The Institute for Healthcare Improvement has developed a ventilator bundle with the following elements that directly target ventilator-associated pneumonia and complications arising from it.
   1. Head of the bed elevation: Maintain the head of the bed elevated (about 30–45 degrees).
   2. Daily sedation interruptions and assessment of readiness to extubate
   3. Stress ulcer prophylaxis
   4. VTE prophylaxis
   5. Daily oral care with chlorhexidine (0.12% oral rinse)

B. Additional methods
   1. Selective decontamination of the digestive tract
      a. It is a short course of antimicrobial therapy aimed at eradicating potential pathogens to minimize ICU-acquired infections.
      b. Selective decontamination is still not routinely performed and is not supported by the guidelines because of the risk of promoting antimicrobial resistance.
   2. Endotracheal tubes coated in an antimicrobial (silver) reduce infection but are cost prohibitive in many centers.

XI. NUTRITION SUPPORT IN CRITICALLY ILL PATIENTS

A. General overview
   1. Many critically ill patients have increased caloric and protein needs, and caloric deficit in these patients leads to excess morbidity (length of stay, infection) and mortality.
   2. Skeletal muscle wasting and weakness occurring during critical illness may lead to prolonged mechanical ventilation and rehabilitation.
   3. Ideally, nutrition should be provided within 24–48 hours of admission to the ICU. Earlier initiation of nutrition is indicated for critically ill patients with hypercatabolic/hypermetabolic conditions (e.g., severe burns, certain traumas).
   4. Route of delivery (EN vs. PN)
      a. In general, EN is preferred to PN in patients with a functional GI tract and who are not malnourished.
      b. American and Canadian guidelines allow hypocaloric feeding during the first 7 days in previously well-nourished patients before consideration of PN. Supplemental PN before 7 days is not recommended in patients without malnutrition.

c. The SSC guidelines suggest early (within 72 hr) initiation of EN in adult patients with sepsis or septic shock. The potential physiologic advantages include maintenance of gut integrity and reduction of the inflammatory response.
d. PN is recommended for patients with extensive small bowel resection, chronic malabsorption, high-output enterocutaneous fistulas, severe malnutrition at baseline, suspected or confirmed GI ischemia, mechanical bowel obstruction, or persistent, severe hemodynamic instability.

B. Estimating nutrition needs
1. Traditional biomarkers of nutrition (albumin, prealbumin, nitrogen balance) are not well validated in critically ill patients.
2. Indirect calorimetry and predictive equations can be used to determine energy needs in critically ill patients.
a. Indirect calorimetry measures the metabolic rate, but it requires special equipment and trained staff and is subject to inaccuracies in some patient populations. Indirect calorimetry also provides a respiratory quotient (RQ), indicating substrate metabolism and allowing modification of macronutrient delivery (e.g., carbohydrates, fats, protein).
b. Several predictive equations for determining caloric goals have been used (e.g., Harris-Benedict, Penn State and modified Penn State, Ireton-Jones, Mifflin, and Swinamer equations). Each comes with variable accuracy rates compared with indirect calorimetry. A single equation has not been shown to be best across various ICU populations.
c. Some guidelines recommend a 25-kcal/kg actual body weight target, but this approach may be too simplistic for most critically ill patients. Current ASPEN guidelines recommend feeding in a range of 12–25 kcal/kg actual body weight for nonobese critically ill adults. Protein should be delivered in the range of 1.2–2 g/kg actual body weight for most ICU patients.
d. Clinicians should use clinical judgment to adjust intake when EN or PN is associated with issues such as intolerance, glycemic variability, or respiratory acidosis.
e. See the references for a review of the usefulness of predictive equations in critically ill patients.
3. Hypocaloric feeding
a. The SSC recommends avoiding mandatory full caloric feeding in the first week, but suggests low-dose feeding (i.e., up to 500 kcal per day), advancing only as tolerated.
b. One study showed that intentional underfeeding (60%–70% of target) of critically ill patients while providing 90%–100% of protein needs showed a significant reduction in hospital mortality.
c. It is recommended that patients with obesity (BMI greater than 30 kg/m^2) can be fed at 60%–70% of target energy requirements or 11–14 kcal/kg actual body weight per day. Protein should be delivered in the range of 2–2.5 g/kg ideal body weight per day.
4. Protein needs
a. The stress response in critical illness increases gluconeogenesis, which cannot be fully suppressed by exogenous glucose.
b. Protein intake of 1.2–2 g/kg of actual body weight is recommended in most critically ill patients.
i. Patients on continuous renal replacement therapy may need up to 2.5 g/kg per day.
ii. Protein restriction is generally not recommended for patients with acute kidney injury who are not receiving renal replacement.
iii. Patients with extensive burn injury may need up to 3 g/kg per day.

C. Enteral nutrition
1. It is important to recognize that the prescribed dose of EN is often not delivered to patients because of interruptions, intolerance, or many other reasons. Use of an EN protocol with guidance on initiation, advancement, and interruptions is essential.

2. "Trophic" feeding, or low-dose enteral feeding with the intent of maintaining GI tract function, is commonly used despite limited evidence.
3. EN can be delivered safely to patients receiving low-dose vasopressors.
4. Gastric versus small bowel (postpyloric) feeding delivery
    a. Delivery of EN directly into the small bowel may be associated with a reduction in pneumonia.
    b. In units where small bowel access is readily available, routine use of small bowel feeding is recommended.
    c. If small bowel access is not readily available, then small bowel feedings should be considered only for patients at high risk of intolerance to EN (on inotropes, continuous infusion of sedatives, or paralytic agents, or patients with high nasogastric drainage) or at high risk for regurgitation and aspiration (nursed in supine position) or who have repeatedly demonstrated intolerance of gastric feeds.
5. Gastric residual volumes
    a. There are no data indicating that interruption of gastric feeding for a specific residual volume prevents morbidity (aspiration pneumonia) in critically ill patients. The guidelines do not recommend routine checking of residual volume to assess aspiration risk. However, residuals may still be checked if there is concern for tolerance or to assess gastric motility, especially in patients with recent bowel surgery.
    b. A residual volume of 250–500 mL is recommended as a point where intervention should occur. Prokinetic agents such as metoclopramide and erythromycin may be given to decrease residuals and enhance gastrointestinal motility.

D. Parenteral nutrition
    1. Parenteral nutrition should be administered via the central vein whenever possible. Peripheral administration is possible, but it must be diluted and can lead to fluid overload with the increased volume of the solution.
    2. Intravenous catheters intended for PN should not be used for any other purpose.
    3. Blood glucose measurements should be taken at least every 4–6 hours for patients receiving PN during initiation and changes in carbohydrate content.

E. Supplemental antioxidants and immunomodulation: Supplemental antioxidants and immunomodulating micronutrients (vitamin E, selenium, fish oils, arginine, glutamine, zinc) are not recommended for general critically ill patients.

F. In addition to the SSC, the American Society of Parenteral and Enteral Nutrition publishes guidelines in conjunction with the Society of Critical Care Medicine (J Parenter Enteral Nutr 2022;46:12-41).

G. Further guidance: See "Fluids, Electrolytes, and Nutrition" chapter.

Patient Case

Questions 14 and 15 pertain to the following case.

A 75-year-old woman (height 65 inches [165 cm], weight 68 kg) who is intubated needs mechanical ventilation for an acute exacerbation of chronic obstructive pulmonary disease. She has a medical history of heart failure and hypertension. Her laboratory values are normal except for a creatinine level of 1.9 mg/dL.

14. Which is the most appropriate recommendation to prevent VTE in this patient?
    A. Initiate intermittent pneumatic compression.
    B. Administer fondaparinux 2.5 mg subcutaneously once daily.
    C. Administer enoxaparin 30 mg subcutaneously twice daily.
    D. Administer heparin 5000 units subcutaneously three times daily.

15. Three days later, the patient continues to need mechanical ventilation. Enteral nutrition has been initiated through her nasogastric feeding tube and has gradually been increased to her goal of 45 mL/hour. Over the past day, her gastric residuals are consistently 300–350 mL. Which statement is most appropriate to optimize this patient's nutrition support?
    A. Change to PN.
    B. Add metoclopramide 5 mg intravenously every 6 hours.
    C. Change feeds to a more concentrated formula.
    D. Decrease tube feeds to 10 mL/hour.

XII. INTRACRANIAL HEMORRHAGE

A. General overview
    1. Intracranial hemorrhage (ICH) is a broad term that encompasses many clinical scenarios. Goals of care are to minimize hemorrhage expansion and to treat associated organ dysfunction, thereby decreasing mortality and improving quality of life.
    2. ICH is classified by the anatomic location of the bleeding.
        a. Intraparenchymal hemorrhage (IPH): Nontraumatic bleeding into the brain parenchyma. IPH is also referred to as intracerebral hemorrhage (ICH).
        b. Subarachnoid hemorrhage (SAH): Bleeding into the space between the pia and arachnoid membranes that can be caused by rupture of a cerebral aneurysm, bleeding from arteriovenous malformations, tumors, amyloid angiopathy, or vasculopathy. Patients may present early on with the classic "worst headache of my life."
        c. Subdural hematoma (SDH) – Bleeding between the dura and arachnoid space
        d. Epidural hematoma (EDH) – Bleeding between the dura and the bone
    3. Subdural and epidural hematomas are usually caused by traumatic injury.
    4. Severity of IPH and resulting neurologic injury guide diagnostic tests, treatment, and prognosis. Commonly used scales include the Glasgow Coma Scale (GCS; Table 19) to assess the level of consciousness and the National Institutes of Health Stroke Scale. Disease-specific scales are also used for SAH and IPH. The Hunt and Hess scale is a qualitative scale that rates patients with SAH from 1 (no symptoms) to 5 (deeply comatose). The Fisher scale rates the amount of blood present in patients with SAH from 1 (no blood visualized) to 4 (diffuse SAH, ICH, or intraventricular hemorrhage present). Because the etiologies of IPH and SAH are different, the ICH score is used for IPH. The ICH score for IPH is a composite score consisting of hemorrhage size, age, site of hemorrhage, and GCS scores and ranges from 0 (best) to 6 (worst).

Table 19. Glasgow Coma Scale

Axes	Score
Eye Opening	
Does not open eyes	1
Opens eyes in response to painful stimuli	2
Opens eyes in response to voice	3
Opens eyes spontaneously	4
Motor Response	
Makes no movements	1
Extension to painful stimuli	2
Abnormal flexion to painful stimuli	3
Flexion or withdrawal to painful stimuli	4
Localizes painful stimuli	5
Obeys commands	6
Verbal Response	
Makes no sounds	1
Incomprehensible sounds	2
Utters appropriate words	3
Confused, disoriented	4
Oriented, converses normally	5

B. Risk factors
   1. Hypertension is the most common risk factor.
   2. Use of fibrinolytic (e.g., alteplase), anticoagulant, and antiplatelet medications
   3. Amyloid angiopathy
   4. Intracranial aneurysm
      a. Rupture may be spontaneous or may result from exertion or hypertension.
      b. Risk factors for rupture include tobacco use, hypertension, cocaine use, a history of SAH, familial history of SAH, large aneurysm size, female sex, connective tissue disease, and older age.
   5. Liver failure–induced coagulopathy
   6. Mycotic aneurysms

C. Management
   1. Blood pressure control
      a. Acute hypertension should be controlled after the diagnosis of SAH. The goal blood pressure has not been definitively established. AHA Guidelines for the Management of Aneurysmal Subarachnoid Hemorrhage recommend balancing the risk of stroke, rebleeding because of hypertension, and maintenance of cerebral perfusion pressure in determining a patient's goal blood pressure. They further state that a goal systolic blood pressure less than 160 mm Hg is reasonable.
      b. Elevated blood pressure is associated with greater hematoma expansion, neurologic deterioration, death, and dependency after ICH. The 2022 AHA/ASA guidelines for managing spontaneous intracerebral hemorrhage recommend acute lowering of SBP to 140 mm Hg for patients with SBP of 150–220 mm Hg and no contraindication to acute blood pressure treatment. Clinicians should use careful titration to ensure smooth and sustained control of blood pressure and avoid large variability to improve functional outcomes. The safety and efficacy data of blood pressure lowering are insufficient for patients with SBP greater than 220 mm Hg, but it may be reasonable to consider aggressive blood pressure reduction with a continuous intravenous agent. INTERACT2 is the largest randomized trial assessing intensive treatment (SBP less than 140 mm Hg) versus

guideline-recommended treatment (SBP less than 180 mm Hg). There was no difference in death or disability at 90 days, but functional outcomes were improved with intensive blood pressure control.

c. Blood pressure should be controlled with an intravenous, titratable agent such as nicardipine or clevidipine. Comparisons of agents and clinical outcomes are lacking. Details on antihypertensive agents are available in the "Acute Care in Cardiology" chapter.

2. Antifibrinolytic therapy
   a. For patients who will have a delay in surgical intervention after an aneurysmal SAH, short-term (less than 72 hours or until angiography) treatment with tranexamic acid or aminocaproic acid (preferred) is reasonable.
   b. The TICH-2 trial evaluating tranexamic acid in acute IPH found no difference in functional status or mortality at 90 days. Because of a lack of benefit, tranexamic acid should not routinely be given in this patient population.
   c. Many different dosing protocols exist for aminocaproic acid and tranexamic acid. Typically, aminocaproic acid is administered as a 4- to 5-g load followed by 1 g/hour. Tranexamic acid is administered as a 1-g load followed by 1 g infused over 8 hours for trauma uses.
   d. Patients who receive antifibrinolytic therapy should be monitored for the development of a VTE.
3. Coagulation factors:
   a. In a study of IPH not caused by anticoagulant therapy, recombinant activated factor VII decreased the size of IPH but did not improve functional outcomes. Meta-analyses showed no benefit on hematoma expansion, functional outcomes, or adverse events. See "Anticoagulation" chapter for information on anticoagulant-related IPH.
4. Seizure prophylaxis
   a. The incidence of seizures after SAH may reach 20%, seen mainly at the time of rupture, with the incidence decreasing after treatment. The use of antiepileptic drugs is controversial and may stem from earlier studies that used primarily phenytoin for prophylaxis. Current guidelines state that prophylaxis can be considered in the immediate posthemorrhage period (first 7 days post-bleed).
   b. Phenytoin is subject to drug interactions, notably with nimodipine (decreasing nimodipine serum concentrations). Both the AHA and the Neurocritical Care Society guidelines recommend against the use of phenytoin because of adverse outcomes.
   c. Levetiracetam is generally considered a safer antiepileptic drug, but data supporting its use are limited.
   d. Compared with SAH, the incidence of seizures in IPH is estimated to be the same or slightly higher; however, seizures can present at the onset or occur late in therapy because of scarring. The 2022 AHA guidelines on IPH recommend against prophylactic anticonvulsants because evidence has not consistently identified benefit or harm with respect to functional outcomes.
5. Vasospasm
   a. Vasospasm is the acute narrowing of the cerebral arteries after aneurysmal SAH. It is most common during the first 7–10 days after aneurysm rupture and the risk typically resolves after 21 days. Untreated, vasospasm leads to delayed cerebral ischemia, a major cause of death and disability.
   b. Oral nimodipine 60 mg every 4 hours for 21 days should be administered in all patients with aneurysmal SAH. Although this agent does not decrease the incidence of vasospasm it has been shown to improve outcomes, especially delayed cerebral ischemia. For patients who are unable to tolerate 60 mg every 4 hours because of hypotension, 30 mg every 2 hours is also an option.
   c. Triple-H therapy (hypertension, hypervolemia, hemodilution) is no longer recommended. Euvolemia should be maintained in all patients. Large volumes of hypotonic fluids should be avoided.
6. Microsurgical clip obliteration by craniotomy and endovascular coiling are both interventions for aneurysmal SAH that should be performed as early as possible. Determination regarding which procedure yields better outcomes is ongoing. Advancements in both approaches have improved the rate of survival and lowered the rate of disability.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: B

This patient's ABG is consistent with metabolic acidosis. The pH is less than 7.40, indicating primary acidosis (Answer C is incorrect). The HCO_3^- and $PaCO_2$ are lower than normal, indicating this is metabolic in origin (Answer D is incorrect). In metabolic acidosis, the decrease in HCO_3^- is the primary disorder. When metabolic acidosis is present, the AG should be calculated to provide additional insight about the potential cause of the disorder. The AG is calculated by subtracting the sum of measured anions (Cl^- and HCO_3^-) from cations (Na^+). This patient's AG (8 mEq/L) is within the normal reference range of 6–12 mEq/L; therefore, it is called a normal AG metabolic acidosis or non-AG metabolic acidosis (Answer B is correct; Answer A is incorrect). *C. difficile*–induced diarrhea is the most likely cause of this patient's acid-base disorder.

2. Answer: D

In patients without chronic obstructive pulmonary disease, a $PaCO_2$ greater than 50 mm Hg is usually an indication for mechanical ventilation, regardless of oxygenation status. Oxygen therapy alone is unlikely to correct this patient's cause of respiratory failure (hypoventilation) (Answer B is incorrect). Similarly, his acid-base disturbance is consistent with a pure acute respiratory acidosis (elevated $PaCO_2$, normal HCO_3-) and is therefore unlikely to respond to HCO_3- (Answer C is incorrect). Acetazolamide is used for metabolic alkalosis (Answer A is incorrect). Given this patient's neurologic status and elevated $PaCO_2$, he should be intubated and transferred to the ICU (Answer D is correct).

3. Answer: C

This patient's ABG is consistent with respiratory acidosis. The pH is below 7.40, indicating acidosis (Answer D is incorrect). The $PaCO_2$ is higher than normal (about 40 mm Hg). In chronic respiratory acidosis, the kidneys conserve HCO_3- (a base) to maintain a normal pH. This patient's compensatory metabolic alkalosis is obvious, given that her serum HCO_3- is 28 mEq/L (which is about 4 mEq/L higher than normal). This patient's elevated HCO- concentration confirms the diagnosis of respiratory acidosis (because the HCO_3- would be less than 24 mEq/L if the acidemia were attributable to a metabolic cause) (Answer C is correct; Answers A and B are incorrect).

4. Answer: C

This patient's hemodynamic profile is most consistent with sepsis (i.e., high CI, low SVR). Her PCWP is consistent with an adequate volume challenge. Because she remains hypotensive despite receiving an adequate fluid load, norepinephrine should be initiated because it is the initial vasopressor of choice in septic shock (Answer C is correct). Dobutamine is an inotropic agent that increases CI, which is adequate in this patient (Answer B is incorrect). If the patient continues to be hypotensive despite adequate fluid resuscitation and use of norepinephrine, angiotensin II can be considered (Answer A is incorrect). Dopamine is an alternative to norepinephrine, but it is not preferred because it is associated with a higher incidence of arrhythmias than norepinephrine (Answer D is incorrect).

5. Answer: B

Calculating an infusion rate is an important role for the pharmacist in code situations. The infusion pump is set to run in milliliters per hour; therefore, the answer should always be in these units. To determine the rate (in milliliters per hour) needed to achieve a 0.05-mcg/kg/minute dose, use the following calculation: concentration of norepinephrine drip: 4 mg/250 mL = 0.016 mg/mL or 16 mcg/mL. Therefore, 75 kg × 0.05 mcg/kg/minute × 60 minutes/1 hour × 1 mL/16 mcg = 14.0625 mL/hour, which is then rounded to 14 mL/hour (Answer B is correct; Answers A, C, and D are incorrect).

6. Answer: B

The patient received adequate fluid resuscitation over several hours, and additional fluids are not needed at this time (Answer D is incorrect). Hydrocortisone is not necessary in this case because the patient is responding to fluid resuscitation and the infusion of norepinephrine, as evidenced by the increase in MAP from 44 mm Hg on arrival at the emergency department to 66 mm Hg after initial resuscitation (Answer A is incorrect). Changing to dopamine is not necessary at this time because the MAP is greater than 65 mm Hg, thus allowing global organ perfusion (Answer C is incorrect). In addition, there is no evidence that a low dose of dopamine will prevent acute kidney injury, and it increases the risk of arrhythmias compared with norepinephrine. The patient's heart rate increased significantly to 148 beats/minute while receiving norepinephrine.

Phenylephrine is an alternative to consider in patients with vasopressor-induced tachyarrhythmias (Answer B is correct).

7. Answer: A

During rewarming, patients can become hypoglycemic. Therefore, a reduction in the insulin infusion is likely, and blood glucose should be monitored more often (Answer A is correct). Neuromuscular blockade assessment can include titrating to a TOF goal; however, a more applicable goal would be the absence of shivering in this patient when the paralytic is briefly interrupted. If the patient is not shivering, consideration should be given to discontinuing the paralytic. Of note, the TOF goal is 2/4 twitches, rather than 0/4, to avoid over-paralysis (Answer B is incorrect). Although discontinuing propofol can facilitate extubation, this should not be done until the patient is no longer paralyzed, is at a normal body temperature, and is ready for ventilator weaning (Answer C is incorrect). Finally, although rewarming can cause hyperkalemia, it is appropriate to monitor K concentrations and treat as needed. It is not appropriate to increase the insulin infusion to prevent hyperkalemia because this could precipitate hypoglycemia during rewarming (Answer D is incorrect).

8. Answer: C

Morphine is an opioid analgesic that provides effective pain control and may also aid in producing slight sedation; however, the patient's existing acute-on-chronic kidney injury would increase likelihood of morphine accumulation due to impaired drug elimination (Answer A is incorrect). Haloperidol is an option for delirium; however, her CAM-ICU is negative, so pharmacologic treatment is not indicated at this time (Answer B is incorrect). Benzodiazepines are not indicated with a RASS score of 0 and should be avoided, when possible, to prevent adverse outcomes such as prolonged mechanical ventilation, increased ICU length of stay, and development of delirium (Answer D is incorrect). Fentanyl intravenous boluses as needed would be an appropriate analgesic for the patient's pain, given that her CPOT is elevated (Answer C is correct).

9. Answer: D

Neuromuscular blocking agents should be titrated to the minimal effective dose. Although a peripheral nerve stimulator may provide information on the level of blockade, the true therapeutic endpoint in all patients is ventilator synchrony (Answer D is correct). Clinicians must recognize that neuromuscular blocking agents do not cross the blood-brain barrier and are not useful as sedatives or analgesics. For this reason, sedatives and analgesics should be optimized before initiating neuromuscular blockade, because titrating to an RASS goal while using neuromuscular blockers is not possible (Answer C is incorrect). Adequate sedation and analgesia must be achieved before initiating a neuromuscular blocker and should continue throughout the treatment. Vecuronium, though inexpensive, accumulates in renal disease and should be avoided (Answer B is incorrect). Analgesics and sedatives should be continued during paralysis (Answer A is incorrect).

10. Answer: B

Although this patient is no longer paralyzed, it would be inappropriate to re-paralyze an obviously agitated patient (Answer A is incorrect) because he or she should first be adequately sedated. Similarly, performing TOF using a peripheral nerve stimulator is unnecessary because it is obvious from the patient's movement that she is not adequately blocked (Answer D is incorrect). It is possible that the patient is agitated and tachycardic because she received neuromuscular agents without adequate sedation or analgesia. Before the paralytic is adjusted, the patient should be given an increased dose of sedation (Answer B is correct). In patients with neuromuscular blockade, it is generally better to err on the side of over-sedation than under-sedation. Dexmedetomidine does not provide the depth of sedation required for neuromuscular blockade (Answer C is incorrect).

11. Answer: B

Gentamicin has pharmacodynamic effects (i.e., inhibits the release of acetylcholine at the nicotinic receptor), which may potentiate the action of neuromuscular-blocking agents (Answer B is correct). Piperacillin/tazobactam and norepinephrine will not prolong the effects of neuromuscular blocking agents (Answers A and C are incorrect). Although hypokalemia can prolong the effects of neuromuscular blocking agents, potassium concentration will not (Answer D is incorrect).

12. Answer: A

Given that the patient is mechanically ventilated, SUP should be administered (Answer D is incorrect).

Antacids such as magnesium hydroxide are not used to prevent stress ulcers (Answer B is incorrect). Sucralfate has been shown inferior to histamine receptor antagonists (Answer C is incorrect). Efficacy of histamine receptor blockers has been shown in several clinical trials, and famotidine would be appropriate to add for this patient (Answer A is correct).

13. Answer: B

This patient's risk factors for SUP (mechanical ventilation and hypoperfusion) are no longer present; therefore, SUP should be discontinued (Answer B is correct). There is no reason to continue SUP until ICU or hospital discharge, and this practice just increases the risk of continuing the SUP in an outpatient without an appropriate indication (Answers A and D are incorrect). A poor appetite is not a risk factor for developing stress-related mucosal disease (Answer C is incorrect).

14. Answer: D

This patient has several risk factors for VTE, including age, respiratory failure, and a history of heart failure. For this reason, intermittent pneumatic compression is insufficient prophylaxis (Answer A is incorrect). Fondaparinux is contraindicated in patients with an estimated CrCl less than 30 mL/minute/1.73 m^2 (Answer B is incorrect). Enoxaparin 30 mg subcutaneously twice daily is not an appropriate dose for this patient, considering her reduced kidney function (Answer C is incorrect). Heparin is appropriate for preventing a VTE in high-risk patients with renal dysfunction (Answer D is correct).

15. Answer: B

Parenteral nutrition is not indicated in patients with a functional GI tract (Answer A is incorrect). Metoclopramide should be considered because the patient's gastric residuals exceed 250 mL (Answer B is correct). Changing to a more concentrated feed would not be indicated unless the patient were volume overloaded (Answer C is incorrect). Enteral nutrition can be continued at the current rate unless the gastric residuals exceed 500 mL despite administering a prokinetic agent (Answer D is incorrect).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: A

Hydrochloric acid infusions are rarely used in practice and are typically reserved for more severe alkalosis (pH greater than 7.55) that is not responding to conventional therapy (Answer C is incorrect). Administering D_5W will provide hydration but will not correct intravascular volume depletion (Answer B is incorrect). Acetazolamide (Answer D) would be a consideration if the metabolic alkalosis persisted after correcting the underlying problem (i.e., volume contraction). This patient's ABG and urine Cl are consistent with a saline-responsive metabolic alkalosis. In critically ill patients, the most common cause of metabolic alkalosis is volume contraction. In this case, the volume contraction is probably caused by overly aggressive diuresis. In patients receiving diuretics, the urine Cl should be measured at least 12–24 hours after the last dose. In addition, the patient is hypotensive with an elevated heart rate, which probably represents hypovolemia. This patient should receive a normal saline infusion (Answer A is correct).

2. Answer: C

If analgesia with fentanyl is adequate, this patient needs a sedative to achieve his RASS goal. Propofol is a sedative that is easily titrated and cost-effective (Answer C is correct). Dexmedetomidine is another safe and effective option, even when used for longer than 24 hours, but it has not been shown superior to propofol in randomized controlled trials (Answer A is incorrect). Furthermore, dexmedetomidine is more expensive than propofol, and a loading dose is not recommended. Lorazepam should be avoided in patients with (or at high risk of) delirium and is not a preferred first-line agent in the guidelines (Answer B is incorrect). Haloperidol is incorrect because the patient is CAM-ICU negative (Answer D is incorrect). Haloperidol can cause further prolongation of the QTc interval and lead to torsades.

3. Answer: C

This patient meets the definition for septic shock. Treatment with 5% albumin is unlikely to offer additional benefit because the patient's MAP is at goal (more than 65 mm Hg) (Answer A is incorrect). Furthermore, colloids are no more effective than crystalloids for fluid resuscitation, and a serum albumin concentration does not predict the efficacy of albumin administration. Hydrocortisone is incorrect because the patient is not persistently hypotensive after receiving fluids and vasopressors (Answer B is incorrect). Although this patient's blood pressure is responding to the infusion of dopamine, the heart rate has increased. Norepinephrine (Answer C) is correct because it has similar efficacy, but with fewer tachyarrhythmias than dopamine. Dopamine should not be reduced because lower doses are not renal protective (Answer D is incorrect).

4. Answer: B

The SSC guidelines recommend adequate fluid resuscitation with either crystalloids or colloids before adding vasopressor agents in patients with sepsis. This patient's CVP, blood pressure, heart rate, and BUN/creatinine ratio indicate that she has intravascular volume depletion and needs immediate volume replacement. Therefore, intravenous fluids with either crystalloid or colloid should be the next therapy added to this patient's regimen. Answers A and C are incorrect because fluid resuscitation should be attempted before adding vasopressors. No data favor colloids over crystalloids, and the substantial increase in cost associated with colloids precludes it from being first line; therefore, Answer D (albumin) is incorrect. Lactated Ringer solution is cost-effective and is a first-line agent per current guidelines (Answer B is correct).

5. Answer: D

Targeted temperature management (i.e., therapeutic hypothermia) improves neurologic recovery and mortality in patients who have had a cardiac arrest (Answer D is correct). Although the patient probably has a metabolic acidosis, administering sodium bicarbonate would not improve outcomes (Answer A is incorrect). Vasopressin is no longer recommended in the ACLS guidelines (Answer B is incorrect). Although acute coronary syndrome is a common cause of cardiac arrest, anticoagulation with heparin would be a consideration after initiating targeted temperature management. A continuous infusion of heparin does not improve mortality in patients with an acute coronary syndrome (Answer C is incorrect). Of note, the induction of hypothermia would not necessarily interfere with treatment plans for acute coronary syndrome (e.g., percutaneous coronary intervention).

6. Answer: D

The cooling phase of therapeutic hypothermia may cause an intracellular shift of potassium, leading to decreased serum potassium on laboratory results. During the rewarming phase, an extracellular shift occurs, placing the patient at risk of hyperkalemia (Answer A is incorrect). Paralytics are not mandatory for shivering prevention during the rewarming phase and should be avoided, if possible (Answer B is incorrect). The rewarming phase of targeted temperature management alone does not place the patient at an increased risk of seizures, so prophylaxis with phenytoin is not required (Answer C is incorrect). Answer D, frequent blood glucose monitoring, is correct.

7. Answer: C

Mechanical ventilation for more than 48 hours is an independent risk factor for stress ulcers; therefore, Answer D is incorrect because the patient has a high risk of developing a stress ulcer and should receive prophylaxis. Antacids such as magnesium hydroxide are not used to prevent stress ulcers because of their need for frequent dosing and increased adverse effects (Answer B is incorrect). Sucralfate was inferior to H2 receptor blockers in preventing clinically significant bleeding (Answer A is incorrect). Histamine-2 receptor blockers and PPIs are the two drug classes commonly used to prevent stress ulcers in critically ill patients (Answer C is correct).

8. Answer: A

The SSC suggests hydrocortisone at a dose of 200 mg per day if fluids and vasopressors cannot restore hemodynamic stability (Answer A is correct; Answer D is incorrect). Although low, random cortisol concentrations predict worse outcomes, there are no data supporting treatment of low cortisol concentrations (Answer C is incorrect). Because of the results of the most recent clinical trial and increased health care costs, a cosyntropin stimulation test is not recommended for patients with septic shock (Answer B is incorrect).

9. Answer: A

There are many ways to estimate nutritional needs in critically ill patients. In general, 25 kcal/kg is an appropriate goal caloric intake per day. The recommended protein intake for medically ill patients in the ICU is 1.2-1.5 g/kg (Answer A is correct). Indirect calorimetry will most closely calculate caloric needs, but it does not provide information on the amount of protein needed (Answer B is incorrect). Feeding at 11–14 kcal/kg is recommended for patients with obesity, but this patient's BMI is less than 30 kg/m^2 (Answer C is incorrect). Prealbumin concentrations have not shown good correlation with nutritional deficits in critically ill patients and are not recommended (Answer D is incorrect).

10. Answer: D

Proton pump inhibitors have been associated with an increase in ventilator-associated pneumonia (Answer A is incorrect). Selective digestive decontamination is effective, but because of its adverse effects and increases in resistant bacteria, it is not in widespread use and is not part of the Institute for Healthcare Improvement ventilator bundle (Answer B is incorrect). Head elevation prevents ventilator-associated pneumonia, but it should be 30–45 degrees (Answer C is incorrect). Chlorhexidine is inexpensive, carries few adverse effects, is easy to administer, and is effective in the prevention of ventilator-associated pneumonia (Answer D).

11. Answer: C

A sliding-scale protocol is inappropriate as the sole therapy for hyperglycemia in the ICU (Answer A is incorrect). The SSC and SCCM guidelines recommend an insulin infusion for two blood glucose values greater than 180 mg/dL (Answer B is incorrect). The ideal blood glucose range for critically ill adults has yet to be determined, but a goal of 80–110 mg/dL will not improve outcomes and may increase mortality (Answer D is incorrect). A target of 140–200 mg/dL prevents hyperglycemia but without an excess risk of hypoglycemia (Answer C is correct).

12. Answer: B

Nimodipine should be administered in all patients with an aneurysmal SAH for 21 days to reduce the risk of delayed cerebral ischemia and improve neurologic outcomes (Answer B is correct). Blood pressure control is important, and the guidelines recommend using a titratable agent such as clevidipine to maintain a goal systolic blood pressure less than 160 mm Hg (Answer C is incorrect). The value of calcium antagonists other than nimodipine for vasospasm remains uncertain (Answers A and D are incorrect).

Fluids, Electrolytes, and Nutrition

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Learning Objectives

1. Recommend an appropriate intravenous fluid regimen and monitoring parameters given a patient clinical scenario.
2. Discuss the appropriate roles and risks of hypertonic and hypotonic saline, treatment regimens, and appropriate monitoring parameters to ensure safe and effective use of these intravenous fluids.
3. Recommend an appropriate pharmacologic treatment plan based on individual patient signs and symptoms of electrolyte abnormalities.
4. Recommend a patient-specific enteral nutrition (EN) or parenteral nutrition (PN) formula, infusion rate, and monitoring parameters based on nutritional needs, comorbidities, and clinical condition.

Abbreviations in This Chapter

AA	amino acid
ADH	antidiuretic hormone
ASPEN	American Society for Parenteral and Enteral Nutrition
BEE	basal energy expenditure
BUN	blood urea nitrogen
D_5W	5% dextrose
EC	extracellular
ECG	electrocardiogram
EN	enteral nutrition
GI	gastrointestinal
IBW	ideal body weight
IC	intracellular
ICU	intensive care unit
IS	interstitial
LBW	lean body weight
MW	molecular weight
NG	nasogastric
PN	parenteral nutrition
SCr	serum creatinine
SIADH	syndrome of inappropriate secretion of antidiuretic hormone
TBF	total body fluid
WBC	white blood cell count

Self-Assessment Questions

Answers and explanations to these questions can be found at the end of this chapter.

1. A 74-year-old woman (weight 72 kg) arrives in the emergency department with a 3-day history of cough, body temperature of 102°F (38.9°C), and lethargy. She has the following vital signs and laboratory values: blood pressure 72/40 mm Hg, heart rate 115 beats/minute, urine output 10 mL/hour, white blood cell count (WBC) 18×10^3 cells/mm^3, hemoglobin 12.5 g/dL, and blood urea nitrogen (BUN)/serum creatinine (SCr) ratio of 28:1.7 mg/dL (baseline SCr 1.2 mg/dL), and blood glucose 82 mg/dL. After a 500-mL fluid bolus of 0.9% sodium chloride, her blood pressure is 80/46 mm Hg and her heart rate is 113 beats/minute. Her chest radiograph is consistent with pneumonia. Her medical history includes coronary artery disease and arthritis. Which is the most appropriate treatment at this time?
   A. Furosemide 40 mg intravenously.
   B. 5% albumin 500 mL infused over 4 hours plus norepinephrine titrated to maintain a systolic blood pressure of 90 mm Hg or higher.
   C. 1000-mL fluid bolus with 5% dextrose (D_5W) and 0.9% sodium chloride.
   D. 1000-mL fluid bolus with 0.9% sodium chloride.

2. An order has been received for 2% sodium chloride. Assume no commercially available product is available. Using 0.9% sodium chloride and 23.4% sodium chloride, first determine how much of each is necessary to prepare 1 L of 2% sodium chloride. Second, calculate the osmolarity of 2% sodium chloride. Finally, determine whether the resultant solution should be administered through a central or peripheral intravenous infusion (molecular weight [MW] of sodium chloride is 58.5, osmotic coefficient is 0.93).
   A. Mix 951 mL of 0.9% sodium chloride plus 49 mL of 23.4% sodium chloride; osmolarity = 635 mOsm/L; peripheral intravenous infusion.
   B. Mix 951 mL of 0.9% sodium chloride plus 49 mL of 23.4% sodium chloride; osmolarity = 954 mOsm/L; central intravenous infusion.
   C. Mix 850 mL of 0.9% sodium chloride plus 150 mL of 23.4% sodium chloride; osmolarity = 954 mOsm/L; central intravenous infusion.
   D. Mix 850 mL of 0.9% sodium chloride plus 150 mL of 23.4% sodium chloride; osmolarity = 513 mOsm/L; peripheral intravenous infusion.

3. A 68-year-old man is admitted to the hospital for worsening shortness of breath during the past 2 weeks caused by heart failure. His serum sodium concentration on admission was 123 mEq/L. Other abnormal laboratory values include brain natriuretic peptide of 850 pg/mL and SCr of 1.7 mg/dL. Chest radiography is consistent with pulmonary edema. The patient weighs 85 kg on admission, which is up 3 kg from his baseline weight. The patient is not experiencing nausea, headache, or mental status changes. The physician orders 3% sodium chloride to treat the hyponatremia. Which recommendation is best?
   A. 3% sodium chloride is an appropriate choice because the hyponatremia is probably acute.
   B. A 250-mL bolus of 3% sodium chloride is appropriate if used in combination with furosemide to prevent volume overload.
   C. 3% sodium chloride is appropriate if the serum sodium does not increase more than 10 mEq/L in 24 hours.
   D. The risks of 3% sodium chloride outweigh the potential benefit for this patient.

4. A 55-year-old man with diabetes and kidney disease has hyperkalemia. His laboratory values include potassium (K^+) 7.2 mEq/L, calcium (Ca^{2+}) 9 mg/dL, albumin 3.5 g/dL, and blood glucose 302 mg/dL. His electrocardiogram (ECG) is abnormal, with peaked T waves. What is the best recommendation for initial treatment?
   A. Regular insulin 10 units intravenously plus 50 g of dextrose intravenously.
   B. 10% calcium gluconate 10 mL intravenously.
   C. Sodium polystyrene sulfonate (Kayexalate) 15 g orally.
   D. Sodium bicarbonate 50 mEq intravenously over 5 minutes.

5. A 68-year-old woman (weight 60 kg) is admitted to the hospital after a cardioembolic stroke. Her medical history is significant for atrial fibrillation, acute myocardial infarction, and diabetes. She has been unconscious for 48 hours. The medical team decides to start providing nutrition. All of her laboratory values, including glucose concentrations, are normal. Although she currently has no enteral access, she does have a peripheral intravenous catheter. Which nutritional regimen is best for this patient?
   A. Insert a central intravenous catheter and initiate parenteral nutrition (PN) containing 60 g of amino acids (AAs), 250 mL of 20% lipid emulsion, 300 g of dextrose, standard electrolytes, multivitamins, and trace elements in a volume of 2000 mL administered over 24 hours.
   B. Insert a central intravenous catheter and initiate PN containing 40 g of AAs, 250 mL of 20% lipid emulsion, 200 g of dextrose, standard electrolytes, multivitamins, and trace elements in a total volume of 2000 mL administered over 24 hours.
   C. Insert a nasogastric (NG) or nasoduodenal feeding tube and infuse an isotonic formula (1 kcal/mL) starting at 25 mL/hour and advance to a goal rate of 65 mL/hour.
   D. Insert a percutaneous endoscopic gastrostomy feeding tube and infuse an isotonic formula (1 kcal/mL) starting at 25 mL/hour and advance to a goal rate of 100 mL/hour.

6. A 70-year-old man is admitted to the hospital with peritonitis caused by severe inflammatory bowel disease. The patient has received adequate fluid resuscitation, and he is prescribed appropriate antibiotics. After several days of the patient being unable to tolerate oral or enteral nutrition, the physician consults the pharmacist to recommend a PN formula to be administered through a central line. The patient is hemodynamically stable, with normal electrolyte concentrations. Weight is 55 kg, BUN/SCr is 20/1.1 mg/dL, and WBC is 17×10^3 cells/mm^3. Assuming that appropriate electrolytes, multivitamins, and trace elements are included, which PN formula, when administered over 24 hours, will best provide this patient adequate calories, AAs, and lipids?
   A. AAs 10% 700 mL, dextrose 30% 325 mL, lipid 20% 500 mL.
   B. AAs 10% 450 mL, dextrose 70% 400 mL, lipid 20% 250 mL.
   C. AAs 10% 800 mL, dextrose 70% 350 mL, lipid 20% 250 mL.

D. AAs 15% 900 mL, dextrose 50% 500 mL, lipid 20% 250 mL.

7. A 59-year-old man has been admitted to the hospital after several days of vomiting and diarrhea. In the emergency department, he had several runs of nonsustained ventricular tachycardia. His plasma potassium on admission is 2.8 mEq/L. After 100 mEq of potassium chloride is infused over 24 hours, his repeated K^+ is 3.2 mEq/L, and he continues to have runs of ventricular tachycardia. Other laboratory values include Na^+ 143 mEq/L, magnesium 1.4 mg/dL, phosphorus 3 mg/dL, Ca^{2+} 9 mg/dL, and ionized Ca^{2+} 1.1 mmol/L. Which treatment would be best to give next?
   A. Administer potassium chloride 20 mEq intravenously over 1 hour each for 4 doses and recheck K^+.
   B. Administer magnesium sulfate as a 2 g slow intravenous infusion over 2 hours.
   C. Administer potassium phosphate 15 mmol intravenously over 4 hours.
   D. Administer calcium gluconate 2 g intravenously over 5 minutes.

8. Which nutritional strategy can best prevent gut mucosal atrophy and subsequent bacterial translocation?
   A. PN enriched with glutamine.
   B. PN enriched with branched-chain AAs.
   C. Enteral nutrition (EN).
   D. Zinc supplementation.

9. A female patient (weight 80 kg) in the intensive care unit has developed acute kidney injury caused by sepsis, and she requires intermittent hemodialysis daily to maintain her BUN/SCr ratio at 49:2.5 mg/dL. Currently, she is receiving appropriate antibiotics and is hemodynamically stable. She has also been receiving PN providing 72 g of AAs per day. What is the best recommendation for this patient's protein intake?
   A. Reduce AAs to 40 g/day.
   B. Reduce AAs to 64 g/day.
   C. Increase AAs to 96 g/day.
   D. Increase AAs to 160 g/day.

BPS Pharmacotherapy Specialty Examination Content.
This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline, tested during the Spring 2024 window:

1. Patient-Centered Pharmacotherapy
   a. 1.1. Develop patient-centered, evidence-based pharmacotherapy plans. Subtasks: 1.1.1–1.1.3, 1.1.6, 1.1.8, 1.1.11, 1.1.16
   b. 1.2. Monitor the patient to ensure safe and effective pharmacotherapy. Subtasks: 1.2.1, 1.2.2, 1.2.4
   c. 1.3. Modify pharmacotherapy plans through ongoing patient assessment. Subtasks: 1.3.1, 1.3.3–1.3.5
2. Application of Evidence to Practice and Education
   a. 2.2. Evaluate pharmacotherapy-related literature and health information. Subtask: 2.2.3
3. Healthcare Systems and Population Health
   a. 3.1. Implement safe and effective medication use systems to improve healthcare system and population-based outcomes. Subtasks: 3.1.2, 3.1.5

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline, tested starting Fall 2024:

1. Patient Care Specialty Areas
   a. 1A. Primary Pharmacotherapy Specialty Areas. Subtask: 1A3
   b. 1B. Secondary Pharmacotherapy Specialty Areas. Subtask: 1B1
   c. 1C. Tertiary Pharmacotherapy Specialty Areas. Subtask: 1C2
2. Therapeutics and Patient Management
   a. 2A. Treatment Planning. Subtasks: 2A1, 2A2, 2A4, 2A5
   b. 2B. Therapeutic Implementation. Subtasks: 2B1, 2B5
   c. 2C. Treatment Outcomes and Monitoring. Subtasks: 2C1–2C3
3. Professional Practice
   a. 3A. Quality of Care. Subtasks: 3A4, 3A5
   b. 3C. Practice Management. Subtasks: 3C1, 3C2

I. FLUID MANAGEMENT

A. Distribution of total body fluid (TBF) (Figure 1)

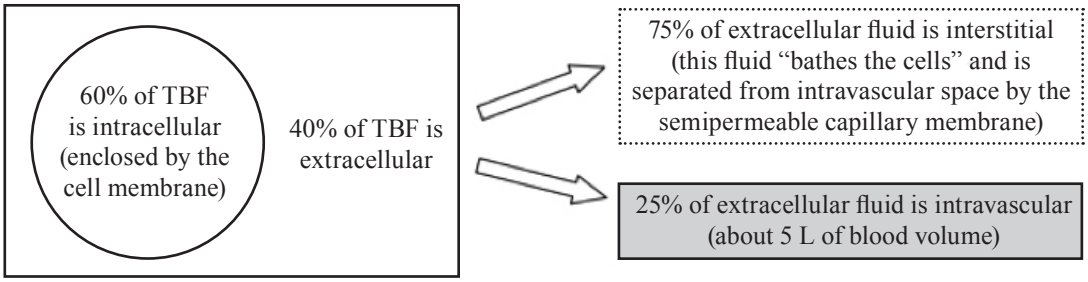

60% of TBF is intracellular (enclosed by the cell membrane)
40% of TBF is extracellular
75% of extracellular fluid is interstitial (this fluid "bathes the cells" and is separated from intravascular space by the semipermeable capillary membrane)
25% of extracellular fluid is intravascular (about 5 L of blood volume)

Figure 1. Distribution of total body fluid.
TBF = total body fluid.

1. Estimated as 60% of lean body weight (LBW) in men and 50% in women; a healthy adult man (weight 70 kg) has about 42 L of fluid
2. Total body water is further divided into intracellular (IC) space and extracellular (EC) space.
   a. About 60% of TBF is IC, and 40% is EC; the IC and EC fluid compartments are separated by cell membranes, which are highly permeable to water.
   b. The EC compartment is also divided into the interstitial (IS) space and the intravascular space; the IS and intravascular fluid compartments are separated by the capillary membrane, which is permeable to almost all solutes except proteins.
      i. 75% of the EC fluid is in the IS space.
      ii. 25% of the EC fluid is in the intravascular space; the EC fluid in the intravascular space is known as *plasma*, and it measures about 3 L; if you also consider about 2 L of fluid found in red blood cells (thus, IC fluid), the total blood volume is about 5 L.
3. The approximate distribution of TBF into the IC and EC compartments with further distribution of the EC fluid into the IS and intravascular compartments is important to remember for determining the distribution of intravenous fluid.

B. Distribution of intravenous fluid (Table 1)

Table 1. Distribution of Intravenous Fluid

Intravenous Fluid	Infused Volume (mL)	Equivalent Intravascular Volume Expansion (mL)
Normal saline	1000	250
Lactated Ringer solution	1000	250
Normosol-R and Plasma-Lyte	1000	250
5% Dextrose	1000	100
Albumin 5%	500	500
Albumin 25%	100	500
Hydroxyethyl starch 6%	500	500

1. Crystalloids are intravenous fluids that can contain water, sodium (Na^+), chloride (Cl^-), and other electrolytes. Lactated Ringer solution is a crystalloid that contains mostly Na^+ and Cl^-, but also lactate, potassium (K^+), and calcium (Ca^{2+}). Normosol-R and Plasma-Lyte are crystalloids that contain mostly Na^+ and Cl^- but also acetate, K^+, and magnesium (Mg^{2+}). D_5W is also a crystalloid, but it should not be used for fluid resuscitation because of the smaller amount of fluid that remains in the intravascular compartment.
    a. Na and Cl^- do not freely cross into cells, but they will distribute evenly in the EC space.
    b. For 0.9% sodium chloride or lactated Ringer solution, only 25% remains in the intravascular space, and 75% distributes in the IS space; therefore, when 1 L of 0.9% sodium chloride or lactated Ringer solution is administered, about 250 mL of fluid remains in the intravascular compartment.
2. D_5W is isosmotic and, because of rapid metabolism, it has the net effect of administering "free" water.
    a. D_5W is metabolized to water and carbon dioxide.
    b. Water can cross any membrane in the body; therefore, it is evenly distributed in TBF ("free" because it is free to cross any membrane).
        i. Many experts avoid administering D_5W whenever possible in patients with neurologic injury and elevated intracranial pressure (ICP) because it can cross into cerebral cells, causing further elevation in ICP.
        ii. Some practitioners avoid the use of D_5W because of the risk of hyperglycemia, although D_5W contains only 5 g of dextrose/100 mL, which is equivalent to 17 kcal/100 mL.
    c. For D_5W, 60% distributes to the IC space and 40% distributes to the EC space. Of the 40% distributed to the EC space, 25% remains in the intravascular space, and 75% distributes to the IS space. Therefore, when 1 L of D_5W is administered intravenously, about 100 mL of fluid remains in the intravascular compartment.
3. Colloids include packed red blood cells, pooled human plasma (5% albumin, 25% albumin, and 5% plasma protein fraction), semisynthetic glucose polymers (dextran), and semisynthetic hydroxyethyl starch (hetastarch).
    a. Colloids are too large to cross the capillary membrane; therefore, they remain primarily in the intravascular space (although a small portion "leaks" into the IS space).
    b. Except for 25% albumin, administering 500 mL of colloid results in a 500-mL intravascular volume expansion.
    c. Because 25% albumin has an oncotic pressure about 5-fold that of normal plasma, it causes a fluid shift from the IS space into the intravascular space. For this reason, 100 mL of 25% albumin results in around 500 mL of intravascular volume expansion. This hyperoncotic solution should generally be avoided in patients requiring fluid resuscitation, because although the intravascular space expands, fluid shifts out of the IS space, potentially causing dehydration. It may be useful in patients who do not require fluid resuscitation but who could benefit from a redistribution of fluid (e.g., ascites, pleural effusions).
    d. Hydroxyethyl starch and dextran products have been associated with coagulopathy and kidney impairment and should be avoided. In addition to acute kidney injury and need for renal replacement therapy, hydroxyethyl starch is associated with increased mortality in critically ill patients (JAMA 2013;309:678-88; N Engl J Med 2012;367:124-34).

C. Fluid Resuscitation
    1. Intravascular fluid depletion can occur because of shock (hypovolemic or septic shock), and it is associated with reduced cardiac function and organ hypoperfusion.
    2. Signs or symptoms (Box 1) usually occur when about 15% (750 mL) of blood volume is lost (e.g., hemorrhage) or shifts out of the intravascular space (e.g., septic shock).

Box 1. Signs and Symptoms of Intravascular Volume Depletion

Tachycardia (HR > 100 beats/minute)
Hypotension (SBP < 80 mm Hg)
Orthostatic changes in HR or BP
Increased BUN/SCr ratio > 20:1
Dry mucous membranes
Decreased skin turgor
Reduced urine output
Dizziness
Improvement in HR and BP after a 500- to 1000-mL fluid bolus

BP = blood pressure; BUN = blood urea nitrogen; HR = heart rate; SBP = systolic blood pressure; SCr = serum creatinine.

3. Fluid resuscitation is indicated for patients with signs or symptoms of intravascular volume depletion.
4. The goal of fluid resuscitation is to restore intravascular volume and to prevent organ hypoperfusion.
5. Because intravascular volume depletion can cause organ dysfunction and death, prompt resuscitation is necessary.
    a. Intravenous fluids are infused rapidly, preferably through a large-bore catheter.
    b. Intravenous fluids are administered as a 500- to 1000-mL bolus, (~30 mL/kg in septic patients) after which the patient is reevaluated; this process is continued as long as signs and symptoms of intravascular volume depletion are improving (Box 1).

Table 2. Content of Common Crystalloid Solutions

	Contents (mEq/L)	**Osmolarity (mOsmol/L)**
Sodium chloride 0.9% (NS)	Na 154 Cl 154	308
Lactated Ringer (LR)	Na 130 Cl 109 K 4 Ca 3 Lactate 28	273
Normosol-R	Na 140 Cl 98 K 5 Mg 3 Acetate 27/Gluconate 23	295

Ca = calcium; Cl = chloride; K = potassium; Mg = magnesium; Na = sodium.

6. Crystalloids are recommended for fluid resuscitation in hypovolemia (Table 2).
    a. Lactated Ringer solution is historically preferred in surgery and trauma patients, but no evidence suggests superiority over normal saline for fluid resuscitation in these settings.
    b. The lactate in lactated Ringer solution is metabolized to bicarbonate, and it can theoretically be useful for metabolic acidosis; however, lactate metabolism is impaired during shock. Thus, lactated Ringer solution may be an ineffective source of bicarbonate.

c. Lactated Ringer solution has been considered to provide a more physiologic amount of Cl (109 mmol/L) than 0.9% sodium chloride (154 mmol/L). In the SMART trial, compared with 0.9% sodium chloride, a balanced fluid regimen (e.g., lactated Ringer solution, Plasma-Lyte 148) resulted in a lower rate of a composite outcome of any cause of death, new renal replacement therapy, and persistent renal dysfunction in intensive care unit (ICU) patients. In the SALT-ED trial of noncritically ill patients, there was no difference found in hospital-free days in non-ICU patients, though balanced fluids reduced major adverse kidney events (N Engl J Med 2018; 378:819-39). However, more recent trials have found no differences between balanced crystalloids and 0.9% sodium chloride. The BaSICS trial, which compared a balanced solution to 0.9% sodium chloride, found no difference in 90-day mortality in critically ill patients (JAMA 2021;326:818-829.) Another trial showed no difference in death or acute kidney injury in ICU patients receiving balanced crystalloids versus 0.9% sodium chloride (N Engl J Med 2022;386:815-826).

7. There is no difference between crystalloids and colloids in the time to achieve fluid resuscitation or in patient outcomes. Colloids have not been shown to be superior to crystalloids, and they are associated with higher cost and some adverse effects. The following are examples of other, although controversial, uses of colloids:
   a. Colloids can be considered after fluid resuscitation with crystalloid (usually 4–6 L) has failed to achieve hemodynamic goals or after clinically significant edema limits the further administration of crystalloid.
   b. Albumin can be considered in patients with a low albumin concentration who have required a large volume of resuscitation fluids or in cirrhotic patients receiving a large volume paracentesis.
   c. Albumin (theoretically, 25% is preferred) can be considered in conjunction with diuretics for patients with clinically significant edema (e.g., pulmonary edema causing respiratory failure) and a low albumin concentration, when appropriately dosed diuretics are ineffective.

D. Maintenance intravenous fluids
   1. Maintenance intravenous fluids are indicated in patients who are unable to tolerate oral fluids.
   2. The goal of maintenance intravenous fluids is to prevent dehydration and to maintain a normal fluid and electrolyte balance.
   3. Maintenance intravenous fluids are typically administered as a continuous infusion through a peripheral or central intravenous catheter.
   4. Common methods of estimating the daily volume in children and adults:
      a. Administer 100 mL/kg for first 10 kg, followed by 50 mL/kg for the next 10 kg (i.e., 1500 mL for the first 20 kg) plus 20 mL/kg for every kilogram greater than 20 kg *or*
      b. Administer 20–40 mL/kg/day (for adults only).
      c. Adjust fluids according to the individual patient's input, output, and estimated insensible loss.
   5. A typical maintenance intravenous fluid is D_5W with 0.45% sodium chloride plus 20–40 mEq of potassium chloride per liter. The potassium chloride content can be adjusted for the individual patient.
   6. If 150 mEq of sodium bicarbonate is added to 850 mL of 0.9% sodium chloride, the resultant solution is equivalent to about 1.6% sodium chloride. When an infusion of 150 mEq of sodium bicarbonate per liter is indicated, it is recommended to add sodium bicarbonate to D_5W or sterile water for injection instead of 0.9% sodium chloride.

Patient Case

Questions 1 and 2 pertain to the following case.

A 65-year-old man (weight 80 kg) with a 3-day history of a body temperature of 102°F (38.9°C), lethargy, and productive cough is hospitalized for community-acquired pneumonia. His medical history includes uncontrolled hypertension and coronary artery disease. His vital signs include heart rate 104 beats/minute, blood pressure 112/68 mm Hg, and body temperature 101.4°F (38.6°C). His urine output is 10 mL/hour, K^+ is 4 mEq/L, BUN is 46 mg/dL, SCr is 1.7 mg/dL, and WBC is 10.4×10^3 cells/mm^3. Other laboratory values are normal.

1. Which is most appropriate at this time?
   A. Furosemide 40 mg intravenously.
   B. Albumin 25% 100 mL intravenously over 60 minutes.
   C. Lactated Ringer solution 1000 mL intravenously over 60 minutes.
   D. D_5W/0.45% sodium chloride plus potassium chloride 20 mEq/L to infuse at 110 mL/hour.

2. After 2 days of appropriate antibiotic treatment, the patient has a WBC of 9×10^3 cells/mm^3, and he is afebrile. His blood pressure is 135/85 mm Hg, and his urine output is 45 mL/hour. His albumin is 3.2 g/dL, BUN is 14 mg/dL, K^+ is 3.9 mEq/L, and SCr is 1.4 mg/dL. All other laboratory values are normal. His appetite is still poor, and he is not taking adequate fluids. He has peripheral intravenous access. Which option is most appropriate to initiate?
   A. Peripheral PN to infuse at 110 mL/hour.
   B. Albumin 5% 500 mL intravenously over 60 minutes.
   C. D_5W/0.45% sodium chloride plus potassium chloride 20 mEq/L to infuse at 110 mL/hour.
   D. Lactated Ringer solution to infuse at 75 mL/hour.

II. OSMOLALITY

A. Plasma osmolality is normally 275–290 mOsm/kg.
   1. Terminology
      a. Osmolality is a measure of the osmoles of solute per kilogram of solvent (Osm/kg), whereas osmolarity is a measure of osmoles of solute per liter of solution (Osm/L).
      b. Plasma osmolarity (mOsm/L) can be calculated as osmolality × 0.995, showing that there is no clinically significant difference between them (i.e., plasma osmolarity is about 1% lower than plasma osmolality).
   2. Plasma osmolality is maintained within a normal range by thirst and secretion of arginine vasopressin (i.e., antidiuretic hormone [ADH]) from the posterior pituitary.
   3. Sodium salts are the primary determinant of plasma osmolality, and they regulate fluid shifts between the IC and EC fluid compartments.
   4. Plasma osmolality (mOsm/kg) can be estimated: $(2 \times Na^+$ mEq/L) + (glucose mg/dL/18) + [(BUN mg/dL) ÷ 2.8].
   5. Increases in plasma osmolality cause an osmotic shift of fluid into the plasma, resulting in cellular dehydration and shrinkage.
   6. Decreases in plasma osmolality cause an osmotic shift of fluid into cells, resulting in cellular overhydration and swelling.

B. Intravenous fluids can be classified by their osmolarity relative to plasma.
   1. Isotonic fluid does not result in a fluid shift between fluid compartments because the osmolarity is similar to plasma.
   2. Hypertonic fluid, such as NaCl 3%, can cause fluid to shift from the IC to the EC compartment, with subsequent cellular dehydration and shrinkage.
   3. Hypotonic fluid, such as NaCl 0.225%, with an osmolarity less than 150 mOsm/L can cause fluid to shift from the EC to the IC compartment, with subsequent cellular overhydration and swelling.
      a. Red blood cell swelling can cause cell rupture (i.e., hemolysis).
      b. Brain cells can swell, causing cerebral edema and herniation; this is most likely to occur with rapid sodium lowering.

C. Definitions
   1. Equivalent weight = Molecular weight (MW) divided by valence.
      a. A milliequivalent (mEq) = 1/1000 of an equivalent.
      b. Examples of equivalent weight are shown in Table 3.
      c. 1 mol = equivalent weight

Table 3. Electrolyte MW, Valence, and Equivalent Weight

Electrolyte	MW	Valence	Equivalent Weight (g)
Sodium	23	1	23
Potassium	39	1	39
Chloride	35.5	1	35.5
Magnesium	24	2	12

MW = molecular weight.

   2. Osmoles = number of particles in a solution (assuming complete dissociation).
      a. A milliosmole = 1/1000 of an osmole.
      b. Examples of osmoles are shown in Table 4.

Table 4. Osmoles

Salt	Osmoles
NaCl	2
KCl	2
$CaCl_2$	3

$CaCl_2$ = calcium chloride; KCl = potassium chloride; NaCl = sodium chloride.

   3. Converting MW to milliequivalents (Box 2)

Box 2. Converting MW to Milliequivalents

Convert 23.4% NaCl (concentrated NaCl) to mEq/mL
MW of NaCl = 23 + 35.5 = 58.5 (add MW of Na + Cl)
$\frac{23.4\text{ g}}{100\text{ mL}} \times \frac{1\text{ equiv}}{58.5\text{ g}} \times \frac{1000\text{ mEq}}{1\text{ equiv}} = 4\text{ mEq/mL}$

MW = molecular weight; NaCl = sodium chloride.

D. Calculating the osmolarity of intravenous fluids in milliosmoles per liter
   1. The osmotic coefficient can be used to calculate the osmolarity of intravenous fluids because salt forms do not completely dissociate in solution. However, commercially available products often have different reported osmolarities than if the osmolarity is calculated using the osmotic coefficient.
      a. With sodium chloride, for example, there is some ionic attraction between Na^+ and Cl, and they do not completely dissociate; rather, they are about 93% dissociated in solution (thus, the osmotic coefficient is 0.93).
      b. In clinical practice and in commercially available products, most do not consider the osmotic coefficient when calculating the osmolarity of sodium chloride or other electrolytes. In reality, the osmotic coefficient is probably not clinically relevant (but it is used in the following examples for completeness).
   2. Normal saline (0.9% sodium chloride) (Table 5)

Table 5. Calculation for Normal Saline Using the Osmotic Coefficient

Molecular Weight	Osmoles	Osmotic Coefficient
58.5 g/mol	2	0.93
$\frac{0.9\text{ g}}{100\text{ mL}} \times \frac{1\text{ mol}}{58.5\text{ g}} \times \frac{2\text{ Osm}}{1\text{ mol}} \times \frac{1000\text{ mOsm}}{1\text{ Osm}} \times \frac{1000\text{ mL}}{1\text{ L}} \times 0.93 = 287\text{ mOsm/L}$		

   3. D_5W (MW 198 g/mol) (Box 3)

Box 3. Calculation for D_5W

$$\frac{5\text{ g} \times}{100\text{ mL}} \times \frac{1\text{ mol}}{198\text{ g}} \times \frac{1000\text{ mOsm}}{1\text{ mol}} \times \frac{1000\text{ mL}}{1\text{ L}} = 252.5\text{ mOsm/L}$$

   4. Osmolarity of D_5W/normal saline using the osmotic coefficient = 252.5 mOsm/L + 287 mOsm/L = 539.5 mOsm/L.
   5. Osmolarity of normal saline + potassium chloride 20 mEq/L (Box 4)

Box 4. Calculation for NS Plus 20 mEq KCl Using the Osmotic Coefficient

Step 1: Convert mEq to weight (g)

$$20\text{ mEq} \times \frac{1\text{ equiv}}{1000\text{ mEq}} \times \frac{74.5\text{ g}}{1\text{ equiv}} = 1.49\text{ g of KCl}$$

Step 2: Calculate mOsm/L

$$\frac{1.49\text{ g}}{\text{L}} \times \frac{1\text{ mol}}{74.5\text{ g}} \times \frac{2\text{ Osm}}{1\text{ mol}} \times \frac{1000\text{ mOsm}}{1\text{ Osm}} = 40\text{ mOsm/L}$$

Step 3: Add osmolarity of NS + KCl = 287 mOsm/L + 40 mOsm/L = 327 mOsm/L

NS = normal saline; KCl = potassium chloride.

III. HYPERTONIC SALINE

A. Typically use 3% (954 mOsm/L), 7.5% (2393 mOsm/L), or 23.4% (7462 mOsm/L). Sodium chloride 3% and 23.4% are available commercially, whereas other concentrations must be extemporaneously prepared.

B. Common uses of hypertonic saline
   1. Hypertonic saline is used in traumatic brain injury to reduce an elevated ICP and thereby increase cerebral perfusion pressure. It is typically used if sustained ICP is greater than 20 mm Hg as measured with an ICP monitor. It is also used for cerebral edema or herniation.
   2. Hypertonic saline is used for symptomatic hyponatremia (symptoms described later in the Hyponatremia section).
      a. Symptoms generally do not occur unless serum sodium is 120 mEq/L or less, and they increase in severity as Na^+ decreases.
      b. Symptoms of severe hyponatremia may include coma and seizures.
      c. In an effort to prevent severe symptoms from occurring, some practitioners treat asymptomatic or moderately symptomatic (e.g., lethargy, confusion) hyponatremia before serum sodium concentrations reach 120 mEq/L or less because of the increased risk of severe symptoms below this concentration.

C. Inappropriate use of hypertonic saline
   1. Chronic asymptomatic hyponatremia
      a. Asymptomatic syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is usually treated with fluid restriction, such as less than 1000 mL of fluid per day.
      b. Hyponatremia typically arises from an excess of free water rather than a sodium deficiency. Therefore, hypertonic saline is typically not useful in the absence of symptoms.
   2. Hyponatremia associated with severe hyperglycemia (pseudohyponatremia; i.e., diabetic ketoacidosis)
      a. Typically, serum sodium decreases in a nonlinear fashion in response to hyperglycemia (i.e., Na^+ decreases by about 1.6 mEq/L for every 100-mg/dL elevation in glucose of 100–400 mg/dL; however, another version of the formula shows that Na^+ decreases by about 2.4 mEq/L for every 100-mg/dL elevation in glucose above 100 mg/dL). Corrected Na^+ = serum Na^+ + [1.6 (glucose – 100)/100]
      b. As hyperglycemia is corrected with insulin, the serum sodium will normalize.
   3. Hyponatremia associated with hypervolemia (i.e., heart failure leads to tissue hypoperfusion, which triggers ADH secretion, causing reabsorption of water from the kidneys and leading to hyponatremia)
      a. In general, this situation is treated with fluid restriction or diuresis.
      b. Symptomatic hyponatremia is uncommon in patients with heart failure.

D. Preparation of hypertonic saline (Commercially available products should be used whenever possible to minimize the risk of error) (Figure 2)

Steps	Example
Choose base solutions	For this example, use concentrated NaCl available as 23.4% vials and sterile water to make 1000 mL of 7.5% HS
Set up alligation	23.4% → 7.5% ← 0
Add and subtract	23.4% → 7.5% ← 0 7.5 parts (from 23.4% NaCl) 15.9 parts (from sterile water) 23.4 parts total
Divide	7.5 parts/23.4 parts = x/1000 mL; x = 320.5 mL of 23.4% NaCl 15.9 parts/23.4 parts = x/1000 mL; x = 679.5 mL of sterile water

Figure 2. Calculations to prepare hypertonic saline.
HS = hypertonic saline; NaCl = sodium chloride.

E. Hypertonic saline dose
   1. Dose examples for traumatic brain injury and other neurological injuries
      a. 3% hypertonic saline 250 mL or 2–4 mL/kg intravenously over 1–15 minutes preferably administered through a central line for elevated ICP or cerebral edema
      b. 23.4% hypertonic saline 30 mL over 20–30 minutes administered through a central line for elevated ICP
         i. Standing orders such as 30 mL every 4–6 hours are sometimes used or may be used as needed for a sustained ICP greater than 20 mm Hg.
         ii. If hypertonic saline is needed for prolonged reduction in ICP, a 3% hypertonic saline continuous infusion may be recommended.
   2. Dose examples for patients with symptomatic hyponatremia
      a. Treatment of patients with symptomatic hyponatremia involves a small but quick increase in serum sodium by 0.75–1 mEq/L/hour to a concentration of 120 mEq/L, though not more than 10–12 mEq in 24 hours. Next, the infusion can be reduced so that Na^+ increases by 0.5 mEq/L/hour. For severe symptoms, it is reasonable to increase serum sodium by up to 2 mEq/L/hour for a short time, as long as the maximum change of 10–12 mEq in 24 hours is not exceeded. If hypertonic saline is used for mild symptoms, a slower change in serum sodium of 0.5 mEq/L/hour would be appropriate, although some would avoid hypertonic saline altogether. Some protocols are more conservative, recommending a maximum change of 8 mEq in 24 hours. If the maximum rate is exceeded in 24 hours or the rate in sodium rise is increasing too rapidly, some practitioners recommend counteracting the quick rise with desmopressin or dextrose 5% in water (more info in hypernatremia section).
      b. Estimate an infusion rate of 3% hypertonic saline by multiplying ideal body weight (IBW) by desired rate of serum sodium increase per hour. (Note: IBW is used to avoid overdosing patients with obesity.)
         i. For example, 70 kg × 1 mEq/L/hour = 70 mL/hour to increase serum sodium by 1 mEq/L in 1 hour. The infusion can be adjusted to achieve goal changes in serum sodium.
         ii. Infusion rate of 3% hypertonic saline is generally 1–2 mL/kg/hour.

iii. In general, 3% hypertonic saline is not recommended in asymptomatic patients; if used in an asymptomatic patient, the administration rate should generally not exceed 0.5–1 mL/kg/hour.

c. Alternatively, some practitioners recommend a 250-mL bolus of 2%–3% hypertonic saline over 30 minutes or 50 mL of 3% hypertonic saline administered as a bolus every 30 minutes for two doses.

F. Administration of hypertonic saline
1. Use central intravenous access because the osmolarity is greater than 900 mOsm/L.
2. If no central line is available, consider using 2% hypertonic saline.
3. Some practitioners use 3% hypertonic saline through a peripheral intravenous access site in an emergency, because the osmolarity is close to the cutoff range for peripheral administration. Recent literature suggests that 3% sodium chloride can safely be administered through a peripheral line (J Neurosci Nurs 2017;49:191-5). If a peripheral site is used, use a large vein and monitor for phlebitis.

G. Clinical goals and monitoring for administering hypertonic saline in patients with symptomatic hyponatremia
1. Goals
   a. Decrease symptoms (described later).
   b. Safe serum sodium achieved usually in the range of 120–125 mEq/L to avoid adverse neurologic outcomes. Note that the immediate goal for patients with symptomatic hyponatremia is not necessarily a normal serum sodium.
   c. Reached maximum safe amount of change in serum sodium
      i. Maximum safe amount of change is generally regarded as 10–12 mEq/L in 24 hours.
      ii. Some practitioners suggest a maximum change of 8 mEq/L in 24 hours.
2. Monitoring of serum sodium every 1–4 hours depending on severity of symptoms

H. Complications of hypertonic saline
1. Osmotic demyelination syndrome (includes central pontine and extrapontine myelinolysis) can occur with rapid correction of hyponatremia.
   a. It is characterized initially by lethargy and affect changes, followed by permanent neurologic damage, including paraparesis, quadriparesis, dysarthria, dysphagia, and coma.
   b. It is more likely to occur with rapid correction of chronic hyponatremia than with acute hyponatremia. This partly explains why it is advisable not to administer hypertonic saline in patients with chronic asymptomatic hyponatremia.
   c. Prevent this complication by avoiding changes in serum sodium of more than 10–12 mEq/L in 24 hours or more than 18 mEq/L in 48 hours.
2. Hypokalemia can occur with large volumes of hypertonic saline.
3. Hyperchloremic non-anion gap metabolic acidosis can result from the administration of chloride salts (i.e., sodium chloride). It can be prevented by administering hypertonic saline in a 1:1 or 2:1 ratio of sodium chloride and sodium acetate or using fluid with less chloride content.
4. Hypernatremia
5. Phlebitis if administered in a peripheral vein
6. Heart failure
   a. Fluid overload can result from initial volume expansion.
   b. Over time, hypertonic saline can have a diuretic effect, leading to intravascular volume depletion.
7. Coagulopathy caused by platelet dysfunction
8. Transient hypotension if hypertonic saline is administered rapidly

I. Other considerations when using hypertonic saline.
    a. Because hypokalemia can cause hyponatremia, remember to correct K^+ depletion if present. As K^+ is replaced, serum sodium will increase.

IV. HYPOTONIC INTRAVENOUS FLUIDS

A. Hypotonic fluids administered intravenously can cause cell hemolysis and patient death.
    1. Albumin 25% diluted with sterile water to make albumin 5% has an osmolarity of about 60 mOsm/L, which can cause hemolysis.
    2. "Quarter normal saline," or 0.225% sodium chloride, has an osmolarity of 77 mOsm/L and can also cause hemolysis.

B. Avoid using intravenous fluid with an osmolarity less than 150 mOsm/L.
    1. Sterile water alone should *never* be administered intravenously.
    2. Some prescribers use hypotonic saline for a patient with hypernatremia.
        a. In reality, a patient with mild hypernatremia generally needs water, not additional Na^+.
        b. Therefore, for patients with hypernatremia, enteral administration of water is preferable.
        c. If the enteral route is unavailable, recommend D_5W administered intravenously, which has a net effect of administering "free" water.

C. Prevent a potentially dangerous error by recommending one of the following alternatives to 0.225% sodium chloride:
    1. Recommend changing 0.225% sodium chloride to D_5W alone or a combination of D_5W and 0.225% sodium chloride.
    2. Alternatively, if there are concerns related to hyperglycemia with using D_5W (50 g of dextrose or 170 kcal/L), recommend using 2.5% dextrose and 0.225% sodium chloride.
    3. Alternatively, potassium chloride can be added to increase osmolarity.
    4. Recommend administering water enterally (by mouth or feeding tube).
    5. If 0.225% sodium chloride is used, recommend use by central venous line.

V. HYPONATREMIA AND HYPO-OSMOLALITY STATES

A. Sodium salts are the primary determinants of plasma osmolality (and subsequent fluid shifts between the IC and EC compartments).
    1. A reduction in serum sodium to less than 136 mEq/L usually correlates with a reduction in plasma osmolality.
    2. Hyponatremia with subsequent hypo-osmolality causes fluid to shift into cells (cellular overhydration). Hypotonic hyponatremia can be divided into three types according to volume status (Table 6).

Table 6. Classification of Hypoosmolar Hyponatremia

	Hypovolemic Hyponatremia	Euvolemic Hyponatremia	Hypervolemic Hyponatremia
Description	Deficit of both Na^+ and fluid, but total Na^+ is decreased more than total body water	Normal total body Na^+ with excess fluid volume (i.e., dilutional)	Excess Na^+ and fluid, but fluid excess predominates
Example	Fluid loss (e.g., emesis, diarrhea, fever), third spacing, renal loss (diuretics), cerebral salt wasting	SIADH, medications	Heart failure, cirrhosis, nephrotic syndrome
Diagnosis	Urine $Na^+ \leq 20$ mEq/L indicates nonrenal loss of Na^+ (e.g., emesis, diarrhea); urine $Na^+ > 20$ mEq/L indicates renal loss of Na^+[a]	Urine osmolality > 100 mOsm/kg (indicates impaired water excretion in presence of plasma osmolality < 275 mOsm/kg); urine sodium > 20 mEq/L[a]	Urine $Na^+ \leq 20$ mEq/L indicates edematous disorders (i.e., heart failure, cirrhosis, nephrotic syndrome); urine $Na^+ > 20$ mEq/L indicates acute or chronic renal failure[a]
Treatment	Fluid resuscitation (see above); in patients with cerebral salt wasting because of a neurologic injury or tumor, hyponatremia can be prevented with sodium chloride tablets or fludrocortisone	If drug-induced SIADH, remove offending agent; fluid restriction; demeclocycline; vasopressin receptor antagonists (e.g., conivaptan, tolvaptan), some institutions use urea	Sodium and water restriction; treat underlying cause; vasopressin receptor antagonists (e.g., conivaptan, tolvaptan), diuretics

Na^+ = sodium; SIADH = syndrome of inappropriate secretion of antidiuretic hormone.
[a]Urine Na+ measurement may be inaccurate if a patient is receiving diuresis.

3. In select cases, hyponatremia is associated with either a normal or an elevated plasma osmolality.
    a. This is known as *pseudohyponatremia* because Na^+ content in the body is not actually reduced. Instead, Na^+ shifts from the EC compartment into the cells in an attempt to maintain plasma osmolality in a normal range. Another adaptation to increased plasma osmolality is the shift of water from inside cells to the EC compartment, which further dilutes the Na^+ concentration.
        i. Severe hyperlipidemia can be associated with a normal or elevated plasma osmolality.
        ii. Severe hyperglycemia (i.e., during diabetic ketoacidosis) is associated with an elevated plasma osmolality.
    b. Once the underlying condition is corrected, Na^+ will shift out of the cells, and hyponatremia will resolve.

B. Causes of hyponatremia
    1. Replacement of lost solute with water
        a. Loss of solute (e.g., vomiting, diarrhea) usually involves the loss of isotonic fluid; therefore, alone, it will not cause hyponatremia.
        b. After the loss of isotonic fluid, hyponatremia can develop when the lost fluid is replaced with water.
        c. A common cause of hyponatremia in hospitals is the postoperative administration of hypotonic fluid.
    2. Volume depletion and organ hypoperfusion stimulate ADH secretion to increase water reabsorption in the collecting tubules, potentially causing hyponatremia.
    3. SIADH and cortisol deficiency are both related to the excessive release of ADH.

4. Medications, including thiazide diuretics, antiepileptic drugs (e.g., carbamazepine, oxcarbazepine), and antidepressants (especially selective serotonin reuptake inhibitors, but also tricyclic antidepressants), can cause hyponatremia. Drug-induced hyponatremia is more likely to occur in older adults and in those who drink large volumes of water.
5. Renal failure impairs the ability to excrete dilute urine, predisposing to hyponatremia.

C. Symptoms of hyponatremia (Table 7)

Table 7. Symptoms of Hyponatremia

Serum Sodium (mEq/L)	Clinical Manifestations
120–125	Nausea, malaise
115–120	Headache, lethargy, obtundation, unsteadiness, confusion
< 115	Delirium, seizure, coma, respiratory arrest, death

1. Symptoms are generally attributable to hypo-osmolality, with subsequent water movement into brain cells causing cerebral edema.
2. If hyponatremia occurs chronically, cerebral cell swelling is prevented by osmotic adaptation.
   a. Solutes such as potassium ions, anions, and small organic compounds move out of brain cells to prevent the osmotic shift of water into brain cells.
   b. For this reason, patients with chronic hyponatremia may show less severe or no symptoms.
3. Neurologic symptoms are related to the rate and degree of change in serum sodium.
4. Acute hyponatremia occurs over 1–3 days.

D. Treatment of hyponatremia
   1. Treat underlying cause.
   2. Raise serum sodium at a safe rate, defined as a change no greater than 10–12 mEq/L in 24 hours (some recommend a change of no more than 8 mEq/L in 24 hours).
   3. Treatment depends on volume status, the presence and severity of symptoms, and the onset of hyponatremia.
      a. If the patient is euvolemic or edematous, there are typically two treatment options:
         i. Fluid restriction (to less than 1000 mL/day) is the typical first-line recommendation for asymptomatic patients. Note that sodium administration is not recommended for asymptomatic patients because it can worsen edema.
         ii. Vasopressin antagonists (e.g., intravenous conivaptan, oral tolvaptan) can be used in euvolemic (i.e., SIADH) or hypervolemic (i.e., heart failure, cirrhosis) patients to promote aquaresis, increase serum sodium, alleviate symptoms, and reduce weight; however, this approach is costly and has not been shown to improve clinical outcomes (i.e., fall prevention, hospitalization, hospital length of stay, quality of life, mortality) in prospective randomized controlled trials. Vasopressin antagonists are substrates and inhibitors of cytochrome P450 3A4 isoenzymes. Monitor for drug interactions with other 3A4 inhibitors that could increase effect and lead to a rapid increase in serum sodium. Fluid restriction in combination with a vasopressin antagonist during the first 24 hours can also increase the risk of overly rapid correction of serum sodium. If needed, fluid restriction can be used after 24 hours. Tolvaptan should not be administered for more than 30 days to minimize risk of liver injury. Monitor for recurrence of hyponatremia once treatment is discontinued. In hypervolemic hyponatremia, diuretics can also be used cautiously.

b. If the patient has intravascular volume depletion, volume must be replaced first with intravenous crystalloids (e.g., 0.9% sodium chloride).
   i. Until intravascular volume is restored, the patient will continue to secrete ADH, causing water reabsorption and subsequent hyponatremia.
   ii. Once intravascular volume is restored, ADH secretion will decrease, causing water to be excreted. This can lead to a rapid correction of serum sodium; careful monitoring is necessary to prevent overly rapid correction.
   iii. Volume status can be assessed by skin turgor, jugular venous pressure, and urine sodium.

c. Once intravascular volume is restored, patients who experienced volume depletion, diuretic-induced hyponatremia, or adrenal insufficiency may still need Na^+.
   i. The amount of Na^+ (in milliequivalents) needed to raise the serum sodium to a safe concentration of about 120 mEq/L (if the serum sodium is less than this) is estimated using LBW as follows: 0.5 (LBW) × (120 − Na^+) for women (multiply LBW by 0.6 for men). LBW has been estimated using weight in kilograms and height in centimeters for men as LBW = [(0.3)(kg) + (0.3)(cm) − 29] or for women as LBW= [(0.3)(kg) + (0.4)(cm) − 43] (J Clin Pathol 1966;19:389-91.)
   ii. Alternatively, this equation can be modified to estimate the Na^+ deficit in the following manner: 0.5 (LBW) × (140 − Na^+) for women (multiply LBW by 0.6 for men). If calculating the Na^+ deficit, it is recommended to administer 25%–50% of the deficit during the first 24 hours to prevent the overly rapid correction of serum sodium.
   iii. Regardless of the method used to estimate Na^+ replacement, the amount of Na^+ administered should be guided by serial serum sodium concentrations (e.g., every 4 hours).

d. Patients with symptomatic hyponatremia should be treated with hypertonic saline (see Hypertonic Saline section).

4. Correct hypokalemia, if present, with hyponatremia.
   a. Hypokalemia will cause a reduction in serum sodium because Na^+ enters cells to account for the reduction in IC K^+ to maintain cellular electroneutrality.
   b. Administration of K^+ will help correct hyponatremia.
   c. Use caution when giving K^+ to prevent overly rapid correction of serum sodium.

Patient Case

Questions 3–5 pertain to the following case.

A 72-year-old woman (weight 60 kg) with a history of hypertension has developed hyponatremia after starting hydrochlorothiazide 3 weeks earlier. She experiences dizziness, fatigue, and nausea. Her serum sodium is 116 mEq/L. Her blood pressure is 86/50 mm Hg, and heart rate is 122 beats/minute.

3. In addition to discontinuing hydrochlorothiazide, which initial treatment regimen is best?
   A. Administer 0.9% sodium chloride infused at 100 mL/hour.
   B. Administer 0.9% sodium chloride 500-mL bolus.
   C. Administer 3% sodium chloride infused at 60 mL/hour.
   D. Administer 23.4% sodium chloride 30-mL bolus as needed.

Patient Case *(Cont'd)*

4. Which is the best treatment goal for the first 24 hours in correcting the patient's serum sodium from her initial value of 116 mEq/L?
   A. Increase Na+ concentration to 140 mEq/L.
   B. Increase Na+ concentration to 132 mEq/L.
   C. Increase Na+ concentration to 126 mEq/L.
   D. Maintain serum sodium of 116–120 mEq/L.

5. One day later, the patient has somewhat improved. Her blood pressure is 122/80 mm Hg, and heart rate is 80 beats/minute. Her serum sodium is 120 mEq/L, and K+ is 3.2 mEq/L; she still feels tired. She is eating a regular diet. Her ECG is normal. Which is the best recommendation?
   A. D_5W/0.9% sodium chloride plus potassium chloride 40 mEq/L to infuse at 100 mL/hour.
   B. 0.9% sodium chloride infused at 100 mL/hour.
   C. 3% sodium chloride infused at 60 mL/hour.
   D. Potassium chloride 20 mEq by mouth every 6 hours for 4 doses.

VI. HYPERNATREMIA AND HYPEROSMOLAL STATES

A. Hyperosmolality with serum sodium greater than 145 mEq/L
   1. The osmotic gradient associated with hypernatremia causes water movement out of cells and into the EC space.
   2. Symptoms are related primarily to the dehydration of brain cells.

B. Causes of hypernatremia
   1. Loss of water because of fever, burns, infection, renal loss (e.g., diabetes insipidus), gastrointestinal (GI) loss
   2. Retention of Na^+ because of the administration of hypertonic saline or any form of Na^+
   3. Certain neurologic injuries receive hypertonic saline to target a higher sodium goal

C. Prevention of hypernatremia through osmoregulation
   1. Plasma osmolality is maintained at 275–290 mOsm/kg, despite changes in water and Na^+ intake.
   2. Hypernatremia is prevented first by the release of ADH, causing water reabsorption.
   3. Hypernatremia is also prevented by thirst.
      a. Hypernatremia occurs primarily in adults with altered mental status who have an impaired thirst response or do not have access to or the ability to ask for water.
      b. Hypernatremia can also occur in infants.

D. Cerebral osmotic adaptation
   1. Similar to patients with hyponatremia, patients with chronic hypernatremia can have cerebral osmotic adaptation.
      a. Brain cells take up solutes, Na^+, and K^+, thus limiting the osmotic gradient between the IC and EC fluid compartments.
      b. This prevents cellular dehydration, and it will increase the brain volume toward a normal value, despite hypernatremia.
   2. Because of osmotic adaptation, patients with chronic hypernatremia may be asymptomatic.

E. Symptoms of hypernatremia are primarily neurologic.
   1. Similar to hyponatremia, the symptoms of hypernatremia are related to the rate of increase in plasma osmolality and the degree of increase in plasma osmolality.
   2. Earlier symptoms include lethargy, weakness, and irritability.
   3. Symptoms can progress to twitching, seizures, coma, and death if serum sodium is greater than 158 mEq/L. However, some neurologic injuries may have higher serum sodium targets.
   4. Cerebral dehydration can cause cerebral vein rupture with subsequent intracerebral or subarachnoid hemorrhage.

F. Treatment of hypernatremia
   1. Rapid correction of chronic hypernatremia can result in cerebral edema, seizures, permanent neurologic damage, and death.
      a. During the development of chronic hypernatremia, brain cells generate "idiogenic osmoles" that restore intracellular water despite the ongoing hypernatremia and protect against brain cell dehydration. If chronic hypernatremia is corrected too rapidly, these idiogenic osmoles predispose to the development of cerebral edema.
   2. In patients with symptomatic hypernatremia, serum sodium should be reduced slowly by no more than 0.5 mEq/L/hour or 12 mEq/L/day.
   3. Treat hypernatremia by replacing water deficit slowly over several days to prevent overly rapid correction of serum sodium.
      a. Using LBW, the estimated water deficit (in liters) is (0.4 × LBW) × [(Serum sodium/140) − 1] in women (multiply LBW by 0.5 in men).
      b. Note that in women and men, total body water is typically about 50% and 60%, respectively, of LBW. Thus, some sources recommend a variation on the earlier equation as follows: Water deficit = (0.5 × LBW) × [(Serum sodium/140) − 1] in women (multiply LBW by 0.6 in men). However, patients with hypernatremia are generally water depleted; thus, the equation using the lower values above (i.e., 40% or 0.4 and 50% or 0.5) is reasonable.
   4. Administer free water orally or intravenously as D_5W.
   5. If concurrent Na^+ and water depletion occur (e.g., vomiting, diarrhea, diuretic-induced depletion), use a combination of D_5W and 0.225% sodium chloride.
   6. If the patient is hypotensive because of volume depletion, first restore intravascular volume with 0.9% sodium chloride to restore tissue perfusion. Normal saline is the preferred crystalloid for fluid resuscitation, and it is still relatively hypotonic in the patient with hypernatremia.
   7. Patients with severe central diabetes insipidus may require desmopressin (DDAVP) (a synthetic analog of ADH) to replace insufficient or absent endogenous ADH. Diabetes insipidus is marked by increased urine output and decreased urine specific gravity.

Patient Case

6. A 74-year-old woman (weight 50 kg) has been receiving isotonic tube feedings at 60 mL/hour for the past 8 days through her gastrostomy feeding tube. She recently had an ischemic stroke; she is responsive but is not able to communicate. Her serum sodium was 142 mg/dL on the day the isotonic formula was initiated, and it has risen steadily to 149, 156, and 159 mg/dL on days 3, 4, and 8, respectively, after the start of the tube feedings. What is the best treatment for her hypernatremia?

   A. Administer sterile water intravenously at 80 mL/hour.

   B. Administer D_5W intravenously at 80 mL/hour.

   C. Administer D_5W/0.225% sodium chloride intravenously at 80 mL/hour.

   D. Administer water by enteral feeding tube 200 mL every 6 hours.

VII. DISORDERS OF K^+

A. Normal plasma potassium concentrations are 3.5–5 mEq/L.

B. K^+ is the primary IC cation (maintains electroneutrality with Na, the primary EC cation).

C. K^+ balance is maintained between the IC and EC compartments by several factors, including the following:
   1. β_2-Adrenergic stimulation (caused by epinephrine) promotes cellular uptake of K^+.
   2. Insulin promotes cellular uptake of K^+.
   3. Plasma potassium concentration directly correlates with movement of K^+ in and out of cells because of passive shifts based on the concentration gradient across the cell membrane. (A normal response to diarrhea-induced hypokalemia is for K^+ to shift out of the cells passively, minimizing the reduction in plasma potassium concentration.)

D. Normal plasma concentrations of K^+ are maintained by renal excretion.

E. Hypokalemia (K^+ concentration less than 3.5 mEq/L)
   1. Causes of hypokalemia
      a. Reduced intake seldom causes hypokalemia because renal excretion is minimized as a result of increased renal tubular absorption.
      b. Increased shift of K^+ into cells can occur with the following:
         i. Alkalosis (respiratory and metabolic)
         ii. Insulin or a carbohydrate load
         iii. β_2-Receptor stimulation caused by stress-induced epinephrine release or administration of a β-agonist (e.g., albuterol, dobutamine)
         iv. Hypothermia
      c. Increased GI losses of K^+ can occur with vomiting, diarrhea, intestinal fistula, or enteral tube drainage, and chronic laxative abuse.
      d. Increased urinary losses can occur with mineralocorticoid excess (e.g., aldosterone) and diuretic use (e.g., loops and thiazides).
      e. Hypomagnesemia is commonly associated with hypokalemia caused by increased renal loss of K^+; correction of plasma potassium requires simultaneous correction of serum magnesium.
   2. Symptoms of hypokalemia generally occur when plasma potassium is less than 3 mEq/L and can include the following:
      a. Muscle weakness occurs most commonly in the lower extremities, but it can progress to the trunk, upper extremities, and respiratory muscles. Muscle weakness in the GI tract can manifest as paralytic ileus, abdominal distention, nausea, vomiting, and constipation.
      b. ECG changes (flattened T waves or elevated U wave) occur.
      c. Cardiac arrhythmias (bradycardia, heart block, ventricular tachycardia, ventricular fibrillation) occur.
      d. Digoxin toxicity can occur despite normal serum digoxin concentrations in the presence of hypokalemia.
      e. Rhabdomyolysis can occur because hypokalemia can cause reduced blood flow to skeletal muscle.
   3. Treatment of hypokalemia
      a. K^+ deficit can be estimated as 200–400 mEq of K^+ for every 1 mEq/L reduction in plasma potassium (assuming a normal distribution of K^+ between EC and IC compartments).
      b. Although the K^+ deficit can be estimated, K^+ replacement is guided by K^+ concentrations; recheck every 2–4 hours if K^+ is less than 3 mEq/L.

c. Potassium chloride is the preferred salt in patients with concurrent metabolic alkalosis because these patients typically lose Cl^- through diuretics or GI loss. This is the most common presentation of hypokalemia.
d. Potassium acetate can be administered intravenously, or potassium bicarbonate can be administered orally for patients with a metabolic acidosis that requires frequent K^+ supplementation.
e. Guidelines for administering K^+ (Table 8)

Table 8. K^+ Replacement

Plasma K^+ (mEq/L)	Treatment[a]	Comments
3–3.5	Oral KCl 40–80 mEq/day if no signs or symptoms (doses > 60 mEq should be divided to avoid GI adverse effects)	Recheck K^+ daily
2.5–3	Oral KCl 120 mEq/day (in divided doses) or IV 60–80 mEq administered at 10–20 mEq/hr if signs or symptoms	Monitor K^+ closely (i.e., 2 hr after infusion)
2–2.5	IV KCl 10–20 mEq/hr until normalized	Consider continuous ECG monitoring
< 2	IV KCl 20–40 mEq/hr until normalized	Requires continuous ECG monitoring

[a]Treatment doses are for patients with normal kidney function and should be reduced for patients with kidney dysfunction or older adults.
ECG = electrocardiogram; GI = gastrointestinal; IV = intravenous; KCl = potassium chloride; K^+ = potassium.

i. Patients without ECG changes or symptoms of hypokalemia can be treated with oral supplementation.
ii. Avoid mixing K^+ in dextrose, which can cause insulin release with a subsequent IC shift of K^+.
iii. To avoid irritation, no more than about 60–80 mEq/L should be administered through a peripheral vein.
iv. Recommended infusion rate is 10–20 mEq/hour to a maximum of 40 mEq/hour.
v. Patients who receive K^+ at rates faster than 20 mEq/hour should be monitored using a continuous ECG.

F. Hyperkalemia
1. Causes of hyperkalemia
a. Increased intake (e.g., potassium infusions/supplementation)
b. Shift of K^+ from the IC to the EC compartment causes hyperkalemia and can occur with the following:
i. Acidosis (respiratory and metabolic)
ii. Insulin deficiency
iii. β-Adrenergic blockade
iv. Digoxin overdose
v. Rewarming after hypothermia (e.g., after cardiac surgery)
vi. Succinylcholine
c. Reduced urinary excretion can occur with:
i. Kidney dysfunction
ii. Intravascular volume depletion
iii. Hypoaldosteronism
iv. K^+-sparing diuretics
v. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers
vi. Trimethoprim

2. Symptoms of hyperkalemia
    a. Muscle weakness or paralysis is caused by changes in neuromuscular conduction; it typically occurs when plasma potassium exceeds 8 mEq/L.
    b. Abnormal cardiac conduction can first manifest as peaked, narrowed T waves (typically, when plasma potassium exceeds 6 mEq/L) and widening of the QRS, and it can progress to ventricular fibrillation and asystole.
    c. Not all patients will experience ECG changes, and the initial manifestation of hyperkalemia can be ventricular fibrillation; thus, consider emergency treatment even in patients with no ECG changes if plasma potassium exceeds 6.5 mEq/L.
    d. Conduction disturbances are increased by hypocalcemia, hyponatremia, acidosis, and rapid elevation in the plasma potassium concentration.
3. Pseudohyperkalemia should be considered if there is no apparent cause or symptoms of hyperkalemia.
    a. Can occur if K^+ is released from cells while or after obtaining the blood specimen, usually because of trauma during venipuncture (hemolysis)
    b. Can result from measurement of the serum rather than the plasma potassium concentration; caused by K^+ release during coagulation
    c. Contamination of blood specimen with potassium-containing intravenous fluids or parenteral nutrition
4. Treatment of hyperkalemia
    a. Patients with an asymptomatic elevation in the plasma potassium who do not have signs or symptoms can be treated with a cation exchange resin (e.g., sodium polystyrene sulfonate) or a potassium binder alone.
    b. Urgent and immediate treatment is required for patients with the following signs or symptoms:
        i. Plasma potassium greater than 6.5 mEq/L
        ii. Severe muscle weakness
        iii. ECG changes
    c. Calcium should be administered intravenously to patients with symptomatic hyperkalemia to prevent hyperkalemia-induced arrhythmias, even if patients demonstrate normocalcemia.
        i. Calcium gluconate can be administered peripherally, and it is preferred to calcium chloride because of a reduced risk of tissue necrosis; dose is 10 mL (equivalent to 1 g, 90 mg elemental, or 4.65 mEq) of 10% calcium gluconate administered over 2–10 minutes. It can be repeated in 5 minutes if no improvement in ECG. Calcium chloride can be used if central intravenous access is available; however, the dose should be adjusted because 10 mL (1 g, 270 mg elemental, or 13.6 mEq) provides 3-fold the amount of elemental Ca as calcium gluconate.
        ii. Onset is within minutes, but duration is short (30–60 minutes).
        iii. It does not reduce plasma potassium, but it antagonizes the effect of K^+ in cardiac conduction cells
        iv. Use in urgent circumstances while waiting for other measures (e.g., insulin and glucose) to lower plasma potassium.
        v. Use caution in patients receiving digoxin because hypercalcemia can precipitate digoxin toxicity, and there are reports of sudden death.
    d. The following treatment options are transient, causing a temporary shift of K^+ from the EC fluid into the cells, and should be used for symptomatic hyperkalemia.
        i. Insulin and glucose
            (a) Dose is typically regular insulin 10 units intravenously plus 25–50 g of dextrose administered as a 50% dextrose intravenous push to prevent hypoglycemia.
            (b) Typically lowers plasma potassium by 0.5–1.5 mEq/L within 1 hour and may last for several hours
            (c) If patients have hyperglycemia, insulin alone can be administered.

(d) More predictable than sodium bicarbonate or β_2-adrenergic agonists in patients with kidney failure
(e) Caution with increased risk of insulin errors when used in emergencies (e.g., incorrectly preparing insulin syringes). Errors involving calculations (100 units/mL) and use of 5- or 10-mL syringes instead of an insulin syringe are possible.
(f) Monitor for signs and symptoms of hypoglycemia even if dextrose is given

ii. Sodium bicarbonate
(a) Dose is 50 mEq of intravenous sodium bicarbonate administered slowly over 5 minutes; it can be repeated after 30 minutes if needed.
(b) It can lower plasma potassium within 30–60 minutes and persist for several hours.
(c) The efficacy of bicarbonate is disputed, and it seems least effective in patients with advanced kidney disease; it may be effective in patients with underlying metabolic acidosis. Sodium bicarbonate use has recently been limited by shortages. Its use should be reserved for other conditions during shortages.

iii. β_2-Adrenergic agonists (e.g., albuterol)
(a) Dose is albuterol 10–20 mg nebulized over 10 minutes or 0.5 mg intravenously (not available in the United States).
(b) The dose will lower plasma potassium by 0.5–1.5 mEq/L.
(c) Onset is within 30 minutes with inhalation.
(d) Avoid use in patients with coronary ischemia because of the risk of tachycardia.
(e) Up to 40% of patients do not respond to inhaled albuterol (especially patients taking β-blockers); therefore, it is not recommended as a single agent for urgent treatment of hyperkalemia. Consider use in combination with insulin.

e. The previous treatment options should be followed by one of the following agents to remove excess K^+ from the body.
i. Diuretics
(a) Loop or thiazide-type diuretics increase K^+ renal excretion.
(b) Ineffective in patients with advanced kidney disease

ii. Cation exchange resins
(a) Sodium polystyrene sulfonate exchanges Na^+ for K^+, resulting in GI excretion of K^+. Exercise caution in patients with kidney disease or heart failure caused by Na^+ (and subsequent fluid) retention.
(b) Because of its slow onset (2 hours) and unpredictable efficacy, sodium polystyrene sulfonate is not indicated for emergency treatment of hyperkalemia.
(c) It was approved by the U.S. Food and Drug Administration in 1958, before demonstrated efficacy was required. No controlled trials show efficacy.
(d) Oral dose of sodium polystyrene sulfonate is 15 g repeated every 6 hours as needed. This can be mixed in 20–100 mL of water or syrup, but it is no longer recommended to mix in 70% sorbitol because of the risk of intestinal necrosis (there are also reports with the premixed 33% sorbitol suspension, but 70% sorbitol appears to have a stronger correlation with intestinal necrosis). Bowel injury is linked to the deposition of drug crystals in the GI tract. Oral sorbitol can prevent constipation associated with the resin; however, the highest risk of intestinal necrosis occurs when administered to patients within 1 week of surgery (occurs in about 1.8% of patients).
(e) Although the oral route is more effective, 30–50 g can also be given as a retention enema mixed in 100–200 mL of an aqueous vehicle (e.g., water, 10% dextrose) that has been warmed to body temperature and kept in the colon for 30–60 minutes, or up to 3 hours. Irrigate the colon afterward. Sorbitol is not recommended as a vehicle for rectal use because of the risk of intestinal necrosis and other serious GI adverse events.

(f) A systematic review found that GI injury is also associated with sodium polystyrene preparations without sorbitol (Am J Med 2013;126:264).

(g) Two potassium binders have largely supplanted sodium polystyrene sulfonate in the treatment of hyperkalemia. As opposed to sodium polystyrene sulfonate, patiromer exchanges Ca^{2+} for K^+, resulting in GI excretion of K^+. As with other binders, caution should be used if patiromer is administered with other medications because it may reduce their absorption. Like sodium polystyrene sulfonate, patiromer should not be used for life-threatening hyperkalemia, because it has a slower onset of action. The other potassium-binding agent, sodium zirconium cyclosilicate, works by exchanging potassium for hydrogen and sodium. Sodium zirconium cyclosilicate has a faster onset of action than patiromer.

iii. Dialysis

(a) It is used when other measures are ineffective or when severe hyperkalemia is present.

(b) Plasma potassium falls by more than 1 mEq/L in the first hour of dialysis and by about 2 mEq/L after 3 hours of dialysis.

(c) Hemodialysis removes K^+ faster than peritoneal dialysis.

(d) Monitor for rebound increase in K^+ after dialysis.

(e) It is used in patients with advanced kidney disease

Patient Case

7. A 61-year-old man comes to the emergency department with shortness of breath and bilateral lower leg edema. Pertinent vital signs and laboratory values include heart rate 30 beats/minute, blood pressure 102/57 mm Hg, K^+ 7.9 mEq/L, Na^+ 139 mEq/L, glucose 278 mg/dL, Ca^{2+} 8.8 mg/dL, digoxin 2.2 ng/mL, BUN 49 mg/dL, and SCr 2.4 mg/dL. His medical history includes heart failure, atrial fibrillation, coronary artery disease, peripheral arterial disease, and diabetes. The patient has peripheral intravenous access and an external pacemaker. Which treatment is most appropriate for lowering this patient's potassium?

A. Calcium gluconate 10 mL intravenously over 2 minutes.

B. Insulin 10 units intravenously.

C. Sodium bicarbonate 50 mEq intravenously over 10 minutes.

D. Albuterol 10 mg nebulized over 10 minutes.

VIII. DISORDERS OF MAGNESIUM HOMEOSTASIS

A. Normal serum magnesium concentration is 1.7–2.3 mg/dL (1.4–1.8 mEq/L or 0.85–1.15 mmol/L).

B. Hypomagnesemia (serum magnesium concentration less than 1.7 mg/dL)

1. Usually associated with impaired intestinal absorption (e.g., ulcerative colitis, diarrhea, pancreatitis, chronic laxative abuse), inadequate intake, hypokalemia, or increased renal excretion (e.g., diuretic use)
   a. Common in hospitalized patients
   b. Often associated with alcoholism and delirium tremens
2. Often occurs concurrently with hypokalemia and hypocalcemia
3. Signs and symptoms
   a. Neuromuscular symptoms include tetany, twitching, and seizures.
   b. Cardiovascular symptoms include arrhythmias, sudden cardiac death, and hypertension.
4. Treatment
   a. Oral supplements (e.g., magnesium oxide, magnesium-containing antacids, or laxatives) can be used for asymptomatic patients; however, treatment is limited by the high frequency of diarrhea.

b. Symptomatic patients should initially be treated with 1–4 g (8–32 mEq) of magnesium sulfate by slow intravenous infusion (about 1 g/hour to avoid hypotension or increased renal excretion because of rapid administration). Initial boluses can be followed by about 0.5 mEq/kg/day added to intravenous fluid and administered as a continuous infusion. For emergency treatment (e.g., torsades), magnesium can be administered by intravenous push. Asymptomatic patients with mild to moderate hypomagnesemia should also be treated with 1–4 g of magnesium sulfate by slow intravenous infusion.
c. Reduce the dose by half in patients with kidney insufficiency.
d. About half of administered magnesium is excreted in the urine; therefore, magnesium replacement can occur over 3–5 days.
e. Intravenous magnesium has also been affected by shortages. Reserve use for symptomatic patients.

C. Hypermagnesemia (serum magnesium greater than 2.3 mg/dL)
1. Rarely occurs and is generally associated with chronic kidney disease
2. Signs and symptoms include nausea, vomiting, bradycardia, hypotension, heart block, asystole, respiratory failure, and death; signs and symptoms rarely occur unless magnesium concentration is greater than 4–5 mg/dL.
3. Treatment
a. Discontinue all magnesium-containing medications.
b. Asymptomatic patients with normal kidney function can be treated with 0.9% sodium chloride and loop diuretics.
c. Symptomatic patients should be treated with 100–200 mg of elemental Ca^{2+} administered intravenously over 5–10 minutes for cardiac stability.
d. Hemodialysis may be needed for patients with kidney disease.

IX. DISORDERS OF PHOSPHORUS HOMEOSTASIS

A. Normal serum phosphorus concentration is 2.5–4.5 mg/dL.

B. Hypophosphatemia (serum phosphorus concentration less than 2.5 mg/dL)
1. Causes of hypophosphatemia
a. Increased renal elimination (e.g., diuretics, glucocorticoids, sodium bicarbonate)
b. Rapidly feeding patients with chronic malnutrition (see "refeeding syndrome" in Parenteral Nutrition section)
c. Respiratory alkalosis
d. Treatment of diabetic ketoacidosis; phosphorus shifts into the IC compartment as diabetic ketoacidosis is corrected
2. Signs and symptoms
a. Tissue hypoxia can occur because of a decrease in oxygen release to peripheral tissues.
b. Neurologic manifestations include confusion, delirium, seizures, and coma.
c. Pulmonary and cardiac symptoms can include respiratory failure, difficulty weaning from mechanical ventilation, heart failure, and arrhythmias.
d. Other organ systems affected include muscle, hematologic, bone, and kidney.
3. Prevention and treatment
a. Prevent hypophosphatemia by supplementing intravenous fluid with 10–30 mmol/L intravenous phosphorus in patients at risk of hypophosphatemia (e.g., malnourished, alcoholism, diabetic ketoacidosis).

b. Oral phosphorus products (e.g., K-Phos Neutral; also contain K^+ and Na) can be used for asymptomatic patients, but they are poorly absorbed.
c. Symptomatic patients typically receive 15–30 mmol and sometimes up to 60 mmol (or 0.5–0.75 mmol/kg of IBW) of phosphorus (sodium phosphate or potassium phosphate) administered intravenously over 3–6 hours (maximum rate is 7.5 mmol/hour). Note: 1 mL of sodium phosphate has 4 mEq of Na^+ and 3 mmol of phosphorus, and 1 mL of potassium phosphate has 4.4 mEq of K^+ and 3 mmol of phosphorus.

4. Phosphate shortages
   a. Reserve phosphate products for patients who need them most (e.g., children, neonates, diabetic ketoacidosis, refeeding syndrome, critically ill patients).
   b. Intravenous fat emulsions contain 15 mmol/L as egg phospholipids; this may be sufficient phosphate for some patients.

C. Hyperphosphatemia
1. It typically occurs in patients with chronic kidney disease or hypoparathyroidism.
2. In general, patients are asymptomatic, but they can have signs and symptoms including hypocalcemia, ECG changes, paresthesias, and vascular calcifications.
3. For treatment, see Treatment of Hyperphosphatemia in the Nephrology chapter.

X. DISORDERS OF CALCIUM HOMEOSTASIS

A. Normal serum calcium concentration is 8.5–10.5 mg/dL (total Ca^{2+} includes bound and unbound Ca^{2+}), and normal ionized calcium is 1.1–1.3 mmol/L (or 4.4–5.3 mg/dL).

B. Distribution of Ca^{2+}
1. EC fluid contains less than 1% of the total body stores of Ca^{2+}; 99% of total body stores of Ca^{2+} are in skeletal bone.
   a. About half of Ca^{2+} in the EC compartment is bound to plasma proteins (primarily albumin).
   b. The active form of Ca^{2+} is the unbound or ionized Ca^{2+}.
2. Ionized Ca^{2+} is regulated by parathyroid hormone, phosphorus, vitamin D, and calcitonin.

C. Hypocalcemia
1. It occurs in patients with chronic kidney disease, hypoparathyroidism, vitamin D deficiency, alcoholism, and hyperphosphatemia, and in patients receiving large amounts of blood products or patients undergoing continuous renal replacement therapy (CRRT [i.e., Ca^{2+} chelates with citrate used as anticoagulation in blood products or for plasmapheresis or CRRT.])
2. Factors that cause an increase in EC Ca^{2+} binding to albumin (e.g., metabolic alkalosis) can cause a reduction in plasma ionized Ca^{2+} concentration, leading to symptomatic hypocalcemia.
3. A low serum albumin will cause a falsely low total serum calcium reading; therefore, an adjustment is necessary. Subtract a patient's serum albumin from a normal serum albumin of 4 g/dL, multiply by 0.8 mg/dL, and then add to the total serum calcium concentration to correct the value. An ionized calcium level may be a more accurate measure of calcium in critically ill patients.
4. Signs and symptoms include tetany, muscle spasms, hypoactive reflexes, anxiety, hallucinations, lethargy, hypotension, and seizures.
5. Treatment
   a. Asymptomatic hypocalcemia associated with hypoalbuminemia is typically associated with normal ionized Ca^{2+} concentrations and therefore does not require treatment.

b. Asymptomatic hypocalcemia can be treated with oral Ca^{2+} supplements at a dose of 2–4 g/day of elemental Ca^{2+} in divided doses; patients may also require vitamin D supplementation.
c. Symptomatic hypocalcemia is treated with 200–300 mg of elemental Ca^{2+} administered intravenously over 5–10 minutes, which in some cases is followed by a continuous infusion (e.g., in patients on CRRT).
    i. Equivalent to 1 g of calcium chloride (273 mg of elemental Ca^{2+}) administered through a central intravenous catheter; peripheral administration of calcium chloride can result in severe limb ischemia
    ii. Equivalent to 2–3 g of calcium gluconate (180–270 mg of elemental Ca^{2+}); preferred for peripheral intravenous administration
    iii. Do not infuse Ca^{2+} at a rate faster than 60 mg of elemental Ca^{2+} per minute; rapid administration, which is not recommended, is associated with hypotension, bradycardia, or asystole.
    iv. The duration of an intravenous dose of Ca^{2+} is ideally 1–2 hours. If a continuous infusion is used, the rate should be 0.5–2 mg/kg/hour of elemental Ca^{2+}.

6. Calcium shortages
    a. If there is a shortage of calcium gluconate, do not add calcium chloride to PN. Use multielectrolyte products in PN, if possible.
    b. The safety of diluted calcium chloride administered peripherally is unknown.

D. Hypercalcemia (serum calcium concentration greater than 10.5 mg/dL) is usually related to malignancy or hyperparathyroidism; see the chapters on Oncology Supportive Care and Nephrology.

XI. ENTERAL NUTRITION

A. Indication and timing: EN is used in patients who are at risk of malnutrition and in whom it is anticipated that oral feedings will be inadequate for 5–7 days. Malnutrition is associated with poor wound healing and increased risk of infection. According to the American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines, well-nourished adults without excessive metabolic stress can usually tolerate little to no nutrition for up to 7 days. The 2021 ASPEN and Society of Critical Care Medicine (SCCM) guidelines for critically ill patients recommend starting enteral feeding within the 48 hours after intensive care unit admission.

B. EN contraindications
1. Complete intestinal obstruction
2. GI fistula (if a feeding tube cannot be placed distal to the fistula or if high-output fistula, which is defined as greater than 500 mL of output per day)
3. Extremely short bowel
4. Severe diarrhea or vomiting
5. Hemodynamic instability or intestinal ischemia
6. Paralytic ileus (however, many patients can be fed through the small bowel, despite an ileus)
7. Absence of bowel sounds is not a contraindication for the provision of EN (i.e., positive bowel sounds are not required for EN initiation), which promotes gut motility

C. EN administration routes
1. Large-bore orogastric and NG tubes
    a. NG tubes are the most common tubes for short-term enteral access.
    b. Orogastric tubes are preferred in patients with nasal or facial trauma or sinusitis, but they are uncomfortable for alert patients.

c. These tubes can be used for stomach decompression in addition to feeding.
d. Prolonged use can cause sinusitis or nasal mucosal ulceration.
e. Patients with a gastric ileus will not tolerate NG feedings, and there is an increased risk of aspiration.

2. Small-bore feeding tubes
   a. These tubes are most commonly placed through the nose, but they can also be placed orally in patients with nasal or facial trauma or sinusitis
   b. They can be placed with the feeding tube tip terminating in the stomach, but because they are smaller and more flexible than NG tubes, they can also be placed past the pyloric sphincter to improve tube feeding tolerance and prevent aspiration.
   c. Nasoduodenal tubes are also smaller than NG tubes, and they can clog from crushed medications if they are not flushed appropriately. Nasojejunal tubes are advanced into the fourth portion of the duodenum or past the ligament of Treitz.
   d. Patients with a gastric ileus or gastroparesis may tolerate feeding by the nasoduodenal or nasojejunal route.
3. Percutaneous endoscopic gastrostomy tubes are placed through the abdominal wall into the stomach for patients requiring long-term feeding; jejunostomy tubes are placed through the abdominal wall into the jejunum, usually to facilitate immediate postoperative or postinjury feeding

D. EN delivery
1. Gravity control refers to delivery with tubing that is fitted with a roller clamp to allow infusion into the stomach as desired.
2. Continuous infusion by an enteral feeding pump is usually used in hospitals because of the lower risk of aspiration compared with bolus feedings; it must be used for duodenal or jejunal feedings.
3. Cyclic feedings are administered continuously for 10–12 hours (overnight) to facilitate patient mobility during the daytime.
4. Intermittent bolus feedings of 100–300 mL for 30–60 minutes every 4–6 hours can be used only for feeding tubes ending in the stomach in stable patients.

E. Benefit of EN
1. EN is preferred in patients with a functional GI tract because it is associated with a lower risk of infection than PN. Early administration of EN is associated with lower rates of infection and shorter lengths of stay.
2. GI mucosal atrophy occurs with an absence of EN or oral nutrition. This can increase the risk of bacterial translocation because of gut bacteria crossing the weakened intestinal barrier.

F. EN formulations
1. Formulations typically contain carbohydrate, fat, protein, electrolytes, water, vitamins, and trace elements in varying amounts.
2. Intact or polymeric formulas are used in patients with normal digestive processes, and they typically contain 1–1.2 kcal/mL.
   a. These are generally inexpensive and an appropriate first choice for many patients.
   b. Some polymeric formulas are concentrated for patients requiring fluid restriction and contain 2 kcal/mL.
   c. Some polymeric formulas are designed for oral administration and are used to supplement the patient's diet.
3. Elemental or semi-elemental formulas are easily digested by patients with impaired digestive capacity or malabsorption (e.g., short bowel, pancreatic insufficiency); they are typically more expensive than polymeric EN.

4. Some EN contains fiber for patients with constipation. Examples include Replete with Fiber and Jevity.
5. Disease-specific EN
    a. EN formulations for patients with renal failure are typically concentrated (i.e., 2 kcal/mL to adhere to fluid restrictions) and can contain differing amounts of protein and electrolytes.
    b. Some EN products designed for patients with respiratory failure have more calories from fat (40%–55% of total calories) and fewer from carbohydrates to reduce the production of CO_2 and facilitate ventilator weaning. However, excessive CO_2 production is caused primarily by overfeeding with total calories rather than the total amount of carbohydrates; therefore, these more expensive formulations may be unnecessary as long as the patient is not being overfed.
    c. EN formulations for patients with diabetes have more calories from fat, fewer calories from carbohydrates, and added fiber to improve glycemic control.
    d. EN formulations for patients with hepatic failure and hepatic encephalopathy contain more branched-chain AAs and fewer aromatic AAs, which may improve encephalopathy (controversial), but are not commonly used.
    e. EN for highly stressed patients (e.g., trauma, burn injury, acute respiratory distress syndrome, sepsis) is enhanced with protein, arginine, glutamine, omega-3 fatty acids, nucleotides, or beta-carotene. These enteral formulations are designed to improve immune function and clinical outcomes. Immune-modulating formulas are recommended for surgical ICU patients in the postoperative setting, but are not recommended for the medical ICU population.
    f. Specialty formulas are not recommended for routine use in a general ICU setting.

G. EN complications
    1. Improper tube placement or displacement
    2. Clogged feeding tubes
        a. Prevent by flushing feeding tube before, between, and after the administration of each drug. The use of liquid formulations of medications, if available, is also recommended.
        b. Unclog feeding tubes with warm water or a pancreatic enzyme solution mixed with oral sodium bicarbonate. Avoid using cola or juice.
    3. Aspiration
        a. Prevent by keeping the head of bed elevated at 30–45 degrees.
        b. Prevent delays in gastric emptying using an EN formula with less fat. Gastric motility can be increased with metoclopramide (5–10 mg intravenously every 6 hours) or erythromycin (250 mg intravenously every 6–8 hours administered until tolerating EN for at least 24 hours). Metoclopramide and erythromycin can be combined, but monitor for diarrhea and tachyphylaxis. Avoid prolonged use of promotility agents because of increased risk of adverse effects.
        c. Administering EN by a feeding tube with the tip terminating beyond the pyloric sphincter can prevent aspiration pneumonia.
        d. Prevent also by initiating EN at a slow rate (e.g., 20 mL/hour) and advance every 4–6 hours as tolerated to goal rate.
    4. Diarrhea
        a. It is more common with products with a higher osmolarity.
        b. Consider other causes of diarrhea such as antibiotic use, infection, lactose intolerance, magnesium, and sorbitol in liquid medication preparations (e.g., liquid acetaminophen).
    5. Constipation can be prevented by adding fiber or bowel stimulation.
    6. Dehydration

7. Hypernatremia occurring when patients are given insufficient water while receiving EN
    a. Patients require about 30 mL/kg/day of water.
    b. Hypernatremia typically occurs in patients with altered mental status who may be unable to communicate thirst.
    c. Calorie-dense (i.e., 1.5 or 2 kcal/mL) EN formulas have less water than products containing 1 kcal/mL; therefore, additional water is needed to prevent hypernatremia.
8. Nasopharyngeal erosions, epistaxis, tracheoesophageal fistula
9. Sinusitis
10. Electrolyte abnormalities most likely to occur in patients who develop refeeding syndrome (discussed later)

Patient Case

8. A 72-year-old woman (weight 65 kg) is switched from a standard enteral formula to a concentrated tube feeding designed for patients with kidney disease, because of hyperkalemia. The patient's baseline and current SCr is 1.7 mg/dL, and her urine output is about 50 mL/hour. The tube feeding is infusing at a goal rate of 35 mL/hour through an NG feeding tube providing 2 kcal/mL, Na^+ 41 mEq/L, and 717 mL/L of water. The patient's serum sodium was 140 mEq/L when the tube feeding was initiated a few days ago, and her Na^+ is now 145 mEq/L. What is the best approach for preventing hypernatremia in this patient?

    A. Change to an EN formula with a lower concentration of Na^+.

    B. Administer intravenous D_5W at 45 mL/hour.

    C. Administer 200 mL of water through a feeding tube every 4 hours.

    D. Reduce the tube feeding to 30 mL/hour.

H. EN monitoring
    1. Blood glucose concentration
    2. Head of bed elevation to 30–45 degrees
    3. GI tolerance
        a. Abdominal pain or distension
        b. Stool frequency and volume
        c. Nausea, vomiting, and diarrhea
        d. Checking gastric residuals is not recommended
    4. Prealbumin weekly (exception: Caution in critically ill patients because it reflects acute-phase response rather than nutritional status); see goals in the Parenteral Nutrition section.
    5. Serum sodium and other electrolytes
    6. Wound healing a sign of adequate nutritional therapy
    7. Other medications that add additional calories (e.g., propofol 1.1 kcal/mL, clevidipine 2 kcal/mL) that require EN rates to be adjusted

I. Developing an EN Regimen (Table 9)

Table 9. Developing an EN Regimen

Steps	Calculation Guide	Example
Determine caloric requirements	25–35 kcal/kg/day *or* estimate energy requirements using an equation such as the Harris-Benedict equation (see more details in Parenteral Nutrition section and Critical Care chapter)	A 60-kg patient would require about 25 kcal/kg/day × 60 kg = 1500 kcal
Choose a formula and assess the calories per milliliter	Usually 1, 1.2, 1.5, or 2 kcal/mL	Choose a 1-kcal/mL formula
Determine infusion rate	(Volume of EN)/24 hr	1500 mL/24 hr = 62.5 mL/hr
Ensure that patient will receive sufficient protein	See product information to find protein content (see protein requirements in Parenteral Nutrition section)	Replete with Fiber provides 64 g/L of protein; therefore, 1500 mL will provide 96 g of protein, or 1.6 g/kg for a patient weighing 60 kg
Ensure that the patient will receive about 30 mL/kg/day of water	See product information to find water content	Replete with Fiber provides 832 mL/L of free water. A patient receiving 1500 mL/day would need about 250 mL of additional water, which can be administered as water flushes through the feeding tube (i.e., 60–70 mL every 6 hr); it is important to consider other fluids that the patient may be receiving

EN = enteral nutrition.

J. Drug administration using enteral access
   1. Liquids are preferable, and they should be diluted with 2–3 times the medication volume with water to decrease osmolality.
   2. Diarrhea can occur with medications having a high osmolality (e.g., medications mixed in sorbitol).
   3. Flush with 20 mL of water before and after each drug administered.
   4. Do not crush sustained-release or enteric-coated pills.
   5. Mix crushed tablets or capsule contents with 10–15 mL of water and administer each drug separately.
   6. It may be necessary to discontinue tube feedings before and after drug administration temporarily to prevent reduced bioavailability (e.g., fluoroquinolones, phenytoin, warfarin, bisphosphonates levothyroxine).
   7. Consider feeding tube location and subsequent drug absorption (e.g., for efficacy, antacids need to be administered into the stomach, not the duodenum).

XII. PARENTERAL NUTRITION

A. Parenteral nutrition (PN) is the administration of intravenous nutrition in patients with a nonfunctioning or inaccessible GI tract in which the duration of PN is anticipated to be at least 7 days (i.e., it is anticipated that the patient will be unable to be fed orally or enterally for at least 7 days). In patients who are at high nutritional risk or severely malnourished and cannot tolerate EN, PN should be initiated as soon as possible.

B. Indications for PN
   1. Severe pancreatitis in patients who cannot tolerate EN
   2. Peritonitis
   3. Severe inflammatory bowel disease (e.g., Crohn disease, ulcerative colitis)
   4. Extensive bowel resection (e.g., short bowel syndrome) causing malabsorption or maldigestion
   5. Complete bowel obstruction
   6. Severe intractable vomiting or diarrhea
   7. Inability to meet full nutritional needs by enteral route alone (can use PN as supplement to EN)

C. Intravenous infusion of PN (Table 10)

Table 10. Estimating the Osmolarity of PN for 1 L of Solution

Nutrient	Estimated Osmolarity
Amino acids	10 mOsm/g
Dextrose	5 mOsm/g
Lipid emulsion 10%–20%	1.3–1.5 mOsm/g
Sodium chloride/acetate	2 mOsm/mEq
Potassium chloride/acetate	2 mOsm/mEq
Calcium gluconate	0.68 mOsm/mL
Magnesium sulfate	4.06 mOsm/mL

PN = parenteral nutrition.

   1. PN should be administered through a central line. This includes any intravenous catheter (e.g., peripherally inserted central catheter, Hickman, Port-A-Cath) where the tip of the catheter is in the superior vena cava or adjacent to the right atrium (femoral catheters should be avoided because of higher risk of venous thrombosis and catheter-related infection).
   2. Peripheral access, which also includes midline catheters, is defined as the catheter tip position outside the central vessels or inferior or superior vena cava. If a peripheral vein is used for PN administration, the osmolarity must not exceed 900 mOsm/L. Peripheral administration can be used in patients with an appropriate indication for PN (see Indications for PN above) when central intravenous access is unavailable and the need for PN is expected to be less than 2 weeks.
      a. Final dextrose concentration should be 10% or less.
      b. Final AA concentration should be 2.5%–4%.
      c. Ca^{2+} concentration should be 5 mEq/L or less.
      d. K^{+} concentration should be 40–60 mEq/L or less.

3. In hospitalized patients, PN is typically administered as a continuous infusion, which is infused over 24 hours.
4. Ambulatory patients may prefer a cyclic PN in which the PN is usually infused for 12 hours.
5. Infusions are generally better tolerated by patients if they are removed from the refrigerator and allowed to come to room temperature before infusion.

D. Types of PN admixtures (Table 11)

Table 11. 2-in-1 PN Compared with 3-in-1 PN

	Advantages	Disadvantages
2-in-1	Longer stability Visual inspection easier 1.2-micron in-line filter recommended for total nutrient admixtures, lipid emulsions, and amino acid–dextrose mixtures	Increased nursing time Requires two sets of tubing and infusion pumps Increased bacterial growth in lipids Maximum 12-hr hang time of separate lipids
3-in-1	Time efficient for nurses Single bag with single tube and infusion pump Decreased vein irritation Inhibited bacterial growth	Shorter stability (1–2 days) Complex compounding (without automated compounder) Visual inspection difficult Emulsion instability Must use 1.2-micron filter, not 0.22-micron Limited compatibility with medications Catheter occlusion more common

1. 2-in-1 refers to PN in which all nutrients are mixed in the same intravenous bag, except for lipids, which are administered by a separate infusion.
   a. Lipids are infused separately, no faster than 0.1 g/kg/hour in adults, using a 1.2-micron filter
   b. Rapid administration of lipids is associated with headache, fever, nausea, hypertriglyceridemia, dyspnea, cyanosis, flushing, sweating, and back or chest pain.
   c. Lipid infusion time should be less than 12 hours because of the potential for microbial growth after this time (growth is reduced when lipids are mixed with dextrose and AAs, as in the 3-in-1 described below, because of reduced pH and increased osmolarity).
   d. Administration tubing for a 2-in-1 should be changed every 24 hours; lipid tubing should be discarded after use (no longer than 12 hours).
2. 3-in-1 (also called *total nutrient admixture*) refers to PN in which all nutrients are mixed in the same intravenous bag.
   a. The stability of a 3-in-1 depends on the pH, which is determined primarily by the final AA concentration (maintain at least 4%).
   b. Do not add concentrated dextrose directly to a lipid emulsion when mixing (see order of mixing discussed later).
   c. Avoid excessive amounts of Ca^{2+} and magnesium (see recommended doses).
   d. Administration tubing for a 3-in-1 should be changed every 24 hours.
   e. Total nutrient admixtures should have a final concentration of amino acids ≥ 4%, monohydrated dextrose ≥ 10%, and injectable lipid emulsion ≥ 2%.

E. Premixed PN
   1. Products available in the United States
      a. Clinimix is a two-compartment bag containing AAs in one compartment and dextrose in the other. This product is available with and without electrolytes. The seal between the two-compartment bag must be broken to mix the AAs and dextrose. Lipids can be added to the container after compartments are mixed or can be administered by Y-site.
      b. ProcalAmine is a solution containing 3% AAs, glycerin (4.3 kcal/g), and electrolytes in a single container, but it is not sufficient for most patients because of insufficient protein and calories.
      c. Kabiven, a newer solution, contains AAs, electrolytes, dextrose, and a lipid emulsion. It is available in a 3-compartment bag for central line administration only. Perikabiven is also available for use for peripheral and central administration.
   2. Patient selection
      a. Evidence is insufficient to show that customized PN is superior to standardized premixed products.
      b. Consider in stable patients who require PN.
      c. Avoid in patients with fluid restriction or high protein needs.
   3. Premixed products require fewer manipulations and have a lower risk of contamination and compounding errors, but they may still require additives (e.g., electrolytes, vitamins, trace elements).

F. Nutritional components of PN formulation
   1. Dextrose used for compounding PN is usually 70%, and it contains 3.4 kcal/g. Glycerol (or glycerin) is another carbohydrate source. Glycerol provides 4.3 kcal/g, and it is used in premixed parenteral products.
   2. Fat emulsion is available as 10% or 20% and contains about 10 kcal/g; it is also available as a 30% formulation for compounding in 3-in-1 only. Smoflipid is available as 20%; it contains soybean oil, medium chain triglycerides, olive oil, and fish oil. Omegaven 10% is also approved for use in the United States. Intralipid is available as a 20% solution.
   3. AAs are available as 3%–20% and provide 4 kcal/g.
   4. Electrolytes are added to maintain physiologic serum concentrations.
   5. Multivitamins and trace elements are added based on the recommended daily amount.

G. Developing a PN regimen for administration through a central intravenous line
   1. Determine caloric requirements.
      a. For patients with a body mass index (BMI) less than 30 kg/m^2, administer 25–35 kcal/kg/day based on actual body weight [BMI = (Weight in kg)/(Height in meters)^2]. It is important not to overfeed patients. The 2021 ASPEN/SCCM guidelines recommend feeding 12–25 kcal/kg during the first 7–10 days of an ICU stay (moderate quality of evidence, weak recommendation). These guidelines also advise clinicians to use their clinical judgment.
      b. If BMI exceeds 30 kg/m^2, can administer 11–14 kcal/kg based on actual body weight or 22–25 kcal/kg based on IBW.
         i. Alternatively, some practitioners advocate using adjusted body weight (ABW) rather than IBW.
         ii. ABW = [(actual weight – IBW) × 0.25] + IBW.
      c. Hypocaloric feeding with high protein in EN and PN involves the administration of about 80% of caloric requirements, and it can be considered in patients with obesity (except in patients with kidney failure requiring hemodialysis and patients with hepatic failure; these patients have increased protein and caloric requirements to maintain a positive nitrogen balance).

   d. One method is to estimate basal energy expenditure (BEE) using the Harris-Benedict equation and multiplying by a stress factor.:
      i. Men: BEE = 66 + 13.7(Weight in kg) + 5(Height in cm) – 6.8(Age in years).
      ii. Women: BEE = 655 + 9.6(Weight in kg) + 1.8(Height in cm) – 4.7(Age in years).
   e. Energy expenditure can also be estimated through indirect calorimetry in critically ill patients (see the Critical Care chapter).
2. Determine fluid requirements.
   a. Usually 30–35 mL/kg/day or 2500–3500 mL/day (for patients without fluid restrictions) to maintain urine output in the range of 0.5–2 mL/kg/hour
   b. Fluid requirements for patients with fluid restrictions (e.g., kidney or cardiac dysfunction) should be individualized.
   c. Do not use PN for fluid replacement but for maintenance fluid only.
3. Determine protein (AA) requirements.
   a. For patients with a BMI less than 30 kg/m^2, protein is usually in the range of 0.8–2 g/kg/day based on actual body weight (may be higher in burn or trauma patients).
      i. Maintenance 0.8–1 g/kg/day
      ii. Moderate stress 1.3–1.5 g/kg/day
      iii. Severe stress 1.5–2 g/kg/day
   b. For patients with a BMI of 30–40 kg/m^2, can give protein 2 g/kg/day based on IBW. For patients with a BMI greater than 40 kg/m^2, can give 2.5 g/kg/day based on IBW.
   c. Patients with chronic kidney dysfunction may need protein restriction to prevent uremia.
      i. Kidney dysfunction without dialysis, 1 g/kg/day
      ii. Kidney failure with intermittent hemodialysis, 1.2–1.5 g/kg/day (1.5–2.5 g/kg/day if continuous renal replacement)
   d. Calories from protein (4 kcal/g) should be included in the total caloric provisions to prevent overfeeding.
   e. For 3-in-1 formulations, the final AA concentration should be around 4% to provide adequate buffering capacity and prevent lipid emulsion destabilization.
   f. Complete protein requirements can be provided on day 1 of PN (i.e., there is no need to slowly titrate up to recommended amount).
4. Calculate remaining nonprotein calories and administer about 20%–30% of total calories as lipid and the remainder as dextrose.
   a. Make sure dextrose rate of administration does not exceed the maximum rate of hepatic oxidation rate of 4–5 mg/kg/minute (may be lower in critically ill patients, so monitor for hyperglycemia and adjust amount of dextrose provided if needed).
      i. Initial dextrose amounts can be in the range of 150–200 g/day.
      ii. May need to reduce to 100–150 g/day initially in patients with diabetes or stress-induced hyperglycemia; increase gradually during first 3–4 days to goals if blood glucose values are less than 140–180 mg/dL.
   b. A higher percentage of calories from lipid (up to 50%–60%, or 2.5 g/kg/day) can be provided for a short time in certain cases (e.g., hyperglycemia, hypercapnia).
   c. Essential fatty acid deficiency can be prevented by supplying approximately 2%–4% of total calories as lipid (can administer lipid emulsion once every 1–2 weeks).

5. Estimate a daily maintenance amount of electrolytes, vitamins, and trace elements (Box 5).

Box 5. Central PN calculations

Example of a central 3-in-1 PN formula for a 70-kg patient hospitalized with ischemic bowel:
1. Total calories estimated as 30 kcal/kg × 70 kg = 2100 kcal
2. Fluid requirements estimated as 1500 mL + (20 mL/kg × 50 kg) = 2500 mL/day (see Fluid Management section for calculation)
3. Estimated protein needs are 1.5 g/kg × 70 kg = 105 g of protein. 4 kcal/g × 105 g = 420 kcal from protein; using 10% AA-based solution, will need 1050 mL to equal 105 g of protein (can round to 1000 mL if this makes compounding easier)
4. Determine calories from fat and dextrose. Total calories needed is 2100 − 420 kcal from AAs = 1680 remaining non–protein calories needed. Administer 25%–30% of total kilocalories as lipid, or about 500 kcal from lipid. Using 20% lipid emulsion, 250 mL is needed to equal 500 kcal (about 2 kcal/mL) Total calories needed is 2100 kcal − 420 kcal (AA) − 500 kcal (lipid) = 1180 kcal needed from dextrose. Assuming 3.4 kcal/g, about 350 g dextrose will be needed. Using a 70% base dextrose solution, 500 mL will be needed to equal 350 g, or 1190 kcal. Calculate the rate of dextrose administration in milligrams per kilogram per minute: [(350 g/24 hr) × (1000 mg/g) × (1 hr/60 min)]/70 kg = 3.5 mg/kg/min. This is an appropriate rate of dextrose administration.
5. The final formula will contain the following: AA 10%, 1050 mL Lipid 20%, 250 mL Dextrose 70%, 500 mL Electrolytes, multivitamins, and trace elements (about 110 mL) Final volume of 1910 mL to infuse at 1910 mL over 24 hours = 80 mL/hr (Final volume assumes the patient is receiving about 600 mL of fluid from other medications to meet fluid requirements)
6. Final concentration of macronutrients in PN is: AA 105 g/1910 mL final volume = 5.5% Lipid 50 g/1910 mL = 2.6% Dextrose 350 g/1910 mL = 18%
7. Final caloric value of PN is: AA 105 g × 4 kcal/g = 420 kcal Lipid 50 g × 10 kcal/g = 500 kcal Dextrose 350 g × 3.4 kcal/g = 1190 kcal Total calories = 420 + 500 + 1190 = 2110 kcal/70 kg = 30 kcal/kg 24% of total calories are provided as lipid

AA = amino acid; PN = parenteral nutrition.

   a. Electrolyte abnormalities should be addressed and corrected before PN is initiated. Avoid replacing electrolyte deficiencies using PN in acutely ill patients.
   b. Maintenance electrolytes (amounts will vary and should be individualized)
      i. Sodium 60–150 mEq/day (1–2 mEq/kg/day)
      ii. K^+ 40–80 mEq/day (1 mEq/kg/day)
      iii. Phosphate 10–40 mmol/day (or 15 mmol/1000 kcal)
      iv. Ca^{2+} 10–15 mEq/day (gluconate is preferred to prevent incompatibilities)
      v. Magnesium 8–20 mEq/day (sulfate form is preferred to Cl to prevent incompatibilities)
      vi. Cl and acetate salt forms to maintain acid-base balance.

vii. Electrolyte adjustment
  (a) Typically, greater amounts of magnesium, phosphorus, and K^+ will be needed during the first few days of PN because of IC shifts.
  (b) Cl and acetate salt forms can be adjusted as needed to maintain acid-base balance (discussed under Monitoring Patients Who Are Receiving PN).

c. Standard trace elements containing selenium, chromium, copper, manganese, and zinc (e.g., MTE-5)
  i. Patients with high-output fistulas, diarrhea, burns, or large open wounds may require additional zinc supplementation.
  ii. Patients with chronic diarrhea, malabsorption, or short-gut syndrome or those with critical illness may require additional selenium supplementation.
  iii. Patients with severe cholestasis should have copper and manganese restricted to prevent accumulation and toxicity because both undergo biliary elimination.

d. Parenteral multivitamin added daily (generally contains 150 mcg of vitamin K).
  i. Additional thiamine (25–100 mg) can be supplemented in patients with a history of alcohol abuse.
  ii. During shortages of parenteral vitamins, can reduce frequency of administration to three times/week or can administer individual vitamins daily (i.e., thiamine, ascorbic acid, niacin, pyridoxine, folic acid) or monthly (i.e., vitamin B_{12})

H. Developing a PN regimen for administration through a peripheral intravenous line (Box 6)

Box 6. Peripheral PN Calculations

Example of a peripheral 3-in-1 PN formula for a 70-kg patient: (remember osmolarity should not exceed 900 mOsm/L)
1. Total calories estimated as 30 kcal/kg × 70 kg = 2100 kcal
2. Fluid requirements estimated as 1500 mL + (20 mL/kg × 50 kg) = 2500 mL/day; prescriber wants PN to contain no more than 2000 mL
3. Calculate amount of dextrose as 2000 mL × 10% = 200 g of maximum dextrose recommended
4. Calculate amount of AA as 2000 mL × 3% = 60 g
5. Add about 500 kcal as lipid (can add more if patient tolerates).
6. Calculate volume so far. Using 70% dextrose, need 286 mL to equal 200 g of dextrose. Using 10% AA, will need 600 mL to equal 60 g. Using 20% lipid, will need 250 mL. Will add electrolytes, trace elements, multivitamins, and enough sterile water for a total volume of 2000 mL
7. Final formula will contain the following: AA 10% 600 mL Lipid 20% 250 mL Dextrose 70% 286 mL Electrolytes, multivitamins, and trace elements Sterile water added for 2000 mL final volume to infuse at 2000 mL/24 hr = 83 mL/hr
8. Final concentration of macronutrients in PN is: AA 60 g/2000 mL final volume = 3% Lipid 50 g/2000 mL = 2.5% Dextrose 200 g/2000 mL = 10%
9. Final caloric value of peripheral PN is: AA 60 g × 4 kcal/g = 240 kcal Lipid 50 g × 10 kcal/g = 500 kcal Dextrose 200 g × 3.4 kcal/g = 680 kcal Total calories = 240 + 500 + 680 = 1420 kcal/70 kg = 20 kcal/kg 35% of total calories are provided as lipid

AA = amino acid; PN = parenteral nutrition.

1. It will probably not meet nutritional needs based on macronutrient and micronutrient concentration restrictions (discussed earlier).
2. For additional calories, increase the percentage of calories administered as lipid.

I. Order of mixing (for manual compounding)
1. Add dextrose, AAs, sterile water.
2. Add phosphate.
3. Add other electrolytes (except Ca) and trace minerals.
4. Mix well to ensure that phosphate is evenly distributed and to prevent precipitation with Ca.
5. Add Ca.
6. Observe for precipitates or contaminants.
7. Add lipid if 3-in-1 formulation. (Note: Do not mix dextrose and lipids directly, because the low pH of dextrose can destabilize the lipid emulsion.)
8. Add vitamins last, as close to the time of PN administration as possible in acute care settings, or just before infusion in patients receiving home PN.

J. Factors associated with Ca^{2+} and phosphate precipitation in PN
1. Increasing pH (more basic) increases the risk of Ca^{2+} and phosphate precipitation.
2. Increasing Ca^{2+} or phosphate concentration increases the risk of precipitation.
   a. If Ca^{2+} concentration is 6 mEq/L or less and phosphate concentration is 30 mmol/L or less, the risk of precipitation is low.
   b. Calcium chloride is more likely to precipitate with phosphate than calcium gluconate; calcium chloride should never be used in compounding PN formulations.
3. The final concentration of AA should be at least 2.5% or greater to prevent Ca^{2+} and phosphate precipitation.
   a. AAs form soluble complexes with Ca^{2+} and phosphate.
   b. AAs provide a buffer system to maintain a lower pH of the PN in an acceptable range to prevent Ca^{2+} or phosphate precipitation.
4. As the temperature increases, the risk of precipitation increases.
   a. PN should be refrigerated if not administered within 24 hours of compounding.
   b. If refrigerated, PN should be administered within 24 hours of rewarming.
5. A 1.2-micron filter (used for a 3-in-1 PN) might not prevent the embolism of a calcium phosphate precipitate, but it should be used anyway to reduce the risk.
6. Order of mixing additives is important to prevent precipitation (see above)
7. The PN should be agitated often during compounding to ensure adequate mixture into solution.

K. Medication additives in PN
1. In general, medications should not be added to PN.
2. Examples of medication incompatibilities are ceftriaxone (precipitates with Ca), phenytoin (can change the pH of PN), medications containing propylene glycol or ethanol as diluents (e.g., furosemide, diazepam, lorazepam, digoxin, phenytoin, etoposide), and iron dextran (trivalent cations destabilize the lipid emulsion in 3-in-1 PN formulations).
3. Incompatible drugs should be administered through a separate intravenous catheter or a separate lumen of a central venous catheter, if possible.
4. If an incompatible intravenous drug is to be administered through the same intravenous catheter as the PN, the PN should be stopped, followed by a compatible flush before and after drug administration. The volume of flush should be sufficient to clear the entire catheter of PN and of drug (typically about 10 mL if flushing the port closest to the patient); for drugs requiring longer infusion times, see below for precautions to prevent rebound hypoglycemia with prolonged interruptions of PN.
5. Only regular insulin is compatible with PN.

L. PN complications
   1. Catheter-related infections are primarily caused by gram-positive organisms and *Candida* spp.
   2. Catheter insertion complications (e.g., pneumothorax, incorrect placement) are possible.
   3. Peripheral venous thrombophlebitis can occur with peripheral catheter placement. Risk is increased by day 4 of catheterization; therefore, site should be rotated every 3 days.
   4. Fluid imbalance can occur.
   5. Acid-base imbalances are usually related to the patient's underlying condition; however, excessive chloride salts in the PN can cause a metabolic acidosis, whereas excessive acetate salts in the PN can cause a metabolic alkalosis.
   6. Hyperglycemia can lead to nosocomial and wound infections.
   7. Gut atrophy can occur.
   8. Overfeeding can cause hepatic steatosis, hypercapnia, hyperglycemia, and azotemia.
   9. Essential fatty acid deficiency can occur.
      a. Symptoms include skin desquamation, hair loss, impaired wound healing, hepatomegaly, thrombocytopenia, fatty liver, and anemia.
      b. It can occur within 1–3 weeks of a lipid-free PN.
   10. Refeeding syndrome can occur in acutely (can include critically ill patients) or chronically malnourished patients when EN or PN is initiated.
      a. Characterized by hypophosphatemia, hypokalemia, hypomagnesemia
      b. Can cause cardiac dysfunction, respiratory dysfunction, and death
      c. Prevention of refeeding syndrome:
         i. Identify patients at risk (e.g., anorexia, alcohol use disorder, cancer, chronically ill, poor nutritional intake for 1–2 weeks, recent unintentional weight loss, malabsorption).
         ii. Initially, provide less than 50% of caloric requirements, and then advance over several days to desired goal.
         iii. Supplement vitamins before initiating PN as well as K^+, phosphate, and magnesium (if needed); monitor daily for at least 1 week; and replace electrolytes as needed (many patients will need aggressive electrolyte replacement during the first week of PN).
   11. Aluminum toxicity
      a. More likely to occur in patients receiving long-term PN or in those with renal dysfunction (aluminum is eliminated renally)
      b. Accumulates in bone and interferes with bone Ca^{2+} uptake, causing osteopenia
      c. Neurotoxicity and microcytic anemia
      d. Contaminates many intravenous electrolytes and intravenous fluids
      e. Aluminum content documented on drug labels
   12. Hepatobiliary disorders (includes steatosis, cholestasis, and gallbladder sludge or stones) can occur with long-term PN administration.
      a. Steatosis (or fatty liver) is associated with overfeeding and a transient elevation in aminotransferase concentration. Although it is usually benign, it can progress to fibrosis or cirrhosis in patients receiving long-term PN.
      b. Cholestasis usually occurs in children, but it can also occur in adults receiving long-term PN and can progress to cirrhosis and liver failure; a conjugated bilirubin concentration greater than 2 mg/dL is the primary sign.
      c. Gallbladder stasis is associated with the development of gallstones, sludge, and cholecystitis; it is more attributable to a lack of EN than to PN administration.
   13. Osteoporosis and osteomalacia can occur in patients receiving long-term PN, and they are associated with higher protein doses (causes increased Ca^{2+} excretion) and chronic metabolic acidosis (because of insufficient acetate).

Patient Case

9. A 43-year-old male trauma patient (height 75 inches, weight 100 kg) was recently extubated and is receiving PN. His PN formula contains 35 kcal/kg, protein 1.2 g/kg, and dextrose infusing at 4.4 mg/kg/minute, and 25% of total calories as lipid. He has gradually developed symptoms of hypercapnia and has developed a respiratory acidosis. The medical team is considering strategies to correct this to avoid reintubation. Which change to the PN formula could best correct this situation?

   A. Change PN to EN and maintain current caloric goals.

   B. Reduce dextrose amount in PN to 3 mg/kg/minute and increase lipid to maintain current caloric goal.

   C. Change electrolytes to the acetate salt in the PN to correct the acid-base imbalance.

   D. Reduce the calories to 25 kcal/kg to prevent overfeeding.

M. Monitoring patients who are receiving PN
   1. Monitor for infection (temperature, WBC, intravenous access site).
   2. Monitor for peripheral vein thrombophlebitis or infiltration (if peripheral access); symptoms include pain, erythema, and tenderness or a palpable cord at the site of the peripheral vein; treat by removing catheter.
   3. Monitor fluid status (weight, edema, vital signs, input and output, temperature).
   4. Monitor nutritional status.
      a. Prealbumin is useful for monitoring the effects of long-term nutrition support in patients who are not critically ill (see EN Monitoring earlier) because it has a shorter half-life than albumin.
         i. Values
            (a) Normal range, 16–40 mg/dL
            (b) Moderate malnutrition, 11–16 mg/dL
            (c) Severe malnutrition, less than 11 mg/dL
         ii. Goal for malnourished patients is an increase of at least 3–5 mg/dL/week until within normal range.
      b. Serum albumin (normal 3.5–5 g/dL) is a poor predictor of nutritional status because it has a long half-life, and concentrations fluctuate during illness.
   5. Monitor for hyperglycemia and hypoglycemia.
      a. A common blood glucose goal is 140–180 mg/dL.
      b. Regular insulin (initially 0.05–0.2 units per gram of dextrose) can be added to the PN for patients using a consistent dosage.
      c. For patients with hyperglycemia or fluctuating insulin dosages, insulin can be supplemented separately from the PN, although this practice varies by practitioner.
      d. Abrupt discontinuation of PN is usually tolerated in patients without diabetes, but rebound hypoglycemia can occur in other patients; avoid by gradually tapering off PN over 1–2 hours. Check blood glucose 30 minutes to 1 hour after discontinuing PN. If PN is discontinued abruptly, rebound hypoglycemia can be avoided by administering 5% or 10% dextrose (may not be necessary if PN is administered through a peripheral catheter).
   6. Monitor for electrolyte and acid-base imbalances. The chloride and acetate salts can be adjusted based on the acid-base status of the patient.
      a. For metabolic alkalosis, Na^+ and K^+ can be administered as the chloride salts.
      b. For metabolic acidosis, Na^+ and K^+ can be administered as the acetate salts (acetate is converted to bicarbonate).
      c. For respiratory acid-base disorders, correct the underlying cause or adjust the ventilator settings as needed.

7. Monitor triglyceride concentrations and withhold lipids in patients with a concentration greater than 400 mg/dL. When calculating lipid and caloric requirements, account for any drugs mixed in a lipid emulsion (e.g., propofol, clevidipine).
8. Monitor hepatic function.
9. Monitor for patient readiness for oral or EN support.
    a. Well-nourished, healthy patients can change immediately from PN to oral or EN.
    b. Older adult, debilitated, or malnourished patients may need a transition period in which oral or EN feedings are gradually increased, coinciding with a reduction in PN.

Patient Cases

10. A patient (weight 70 kg) receives propofol at 45 mcg/kg/minute. Propofol is available at a concentration of 10 mg/mL and is mixed in a 10% lipid emulsion. Assuming the patient is receiving this infusion rate for 24 hours, which best approximates the total calories provided by the propofol infusion in a 24-hour period?
    A. 200 kcal.
    B. 250 kcal.
    C. 300 kcal.
    D. 500 kcal.

11. A patient (weight 65 kg) is receiving PN after abdominal surgery. The PN contains about 1600 kcal, including 100 g of protein, 500 kcal as lipid, and 200 g of dextrose. The following additives are also included in a 24-hour infusion of PN: sodium chloride 50 mEq, sodium acetate 100 mEq, potassium acetate 60 mEq, sodium phosphate 30 mmol, magnesium sulfate 12 mEq, calcium gluconate 10 mEq/day, multivitamins 10 mL, and trace elements 3 mL. The patient has an NG tube in place that is suctioning 400–500 mL/day, which is being replaced with an infusion of 0.9% sodium chloride. After 48 hours of PN, the patient has the following laboratory values: Na^+ 140 mEq/L, K^+ 3.8 mEq/L, Cl^- 93 mEq/L, serum bicarbonate 35 mEq/L, pH 7.5, PCO_2 47 mm Hg, and bicarbonate 36 mEq/L. Which adjustment to the PN formula is best at this time?
    A. Increase lipids to provide 750 kcal and reduce dextrose to 130 g.
    B. Increase sodium acetate to 150 mEq/day and discontinue sodium chloride.
    C. Increase sodium chloride to 150 mEq/day and discontinue sodium acetate.
    D. Add sodium bicarbonate 50 mEq to PN.

Questions 12 and 13 pertain to the following case.
A 75-year-old woman (weight 50 kg) is receiving PN after an extensive bowel resection. She is expected to require about 1 week of PN. She is receiving the following macronutrients in her formula: 70% dextrose 300 mL, 20% lipid 150 mL, and 10% AA 750 mL.

12. If these macronutrients are infused over 24 hours, which choice most closely approximates the total calories this patient is receiving daily?
    A. 20 kcal/kg.
    B. 26 kcal/kg.
    C. 30 kcal/kg.
    D. 35 kcal/kg.

Patient Cases (*Cont'd*)

13. The patient has received the PN formula for 3 days. Her blood glucose concentrations have ranged from 220 to 280 mg/dL. She has orders for the following sliding scale of regular insulin: blood glucose 200–250 mg/dL, give 2 units; blood glucose 251–300 mg/dL, give 4 units; and blood glucose 301–350 mg/dL, give 6 units. She has been receiving 14–16 units of insulin daily through the sliding-scale orders. Her medical history is significant for hypertension, diabetes, chronic obstructive pulmonary disease, and colon cancer. Treatment was recently initiated with methylprednisolone 60 mg intravenously every 6 hours for a chronic obstructive pulmonary disease exacerbation. Today, the dose will be reduced to 40 mg intravenously every 8 hours. What is the best recommendation for better control of this patient's blood glucose?

    A. Add insulin glargine 10–20 units/day to PN.

    B. Change 70% dextrose in PN to D_5W.

    C. Increase the sliding-scale insulin to 4 units for blood glucose 200–250 mg/dL, 8 units for blood glucose 251–300 mg/dL, and 12 units for blood glucose 301–350 mg/dL.

    D. Add neutral protamine Hagedorn insulin (NPH) 5 units subcutaneously every 12 hours.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: C

Although this patient's blood pressure is not necessarily low, it is probably low compared with his baseline, considering his history of hypertension. In addition to his low blood pressure, his other signs and symptoms of intravascular volume depletion include an elevated BUN/SCr ratio, an elevated heart rate, and a reduced urine output. Crystalloids or colloids are appropriate fluids for resuscitation, making lactated Ringer solution (Answer C) the best option. Furosemide (Answer A) may increase his urine output, but at the cost of further depleting the intravascular volume. Albumin 25% (Answer B) should be avoided for fluid resuscitation because it causes a shift of fluid from the IS space into the intravascular space, which can potentiate his dehydration. Answer D would be appropriate for a maintenance infusion; however, D_5W/0.45% sodium chloride plus potassium chloride 20 mEq/L would not provide optimal replacement of the intravascular space, given the distribution in TBF.

2. Answer: C

This patient has no signs or symptoms of intravascular volume depletion; therefore, he does not require fluid resuscitation. Because he is not taking adequate fluids by mouth, he should be given maintenance intravenous fluid to prevent dehydration and electrolyte imbalances. This is typically accomplished by a combination of free water and 0.45% sodium chloride with K^+ (Answer C). The infusion rate is calculated as 1500 mL + (60 kg × 20 mL/kg) = 2700 mL/24 hours, or about 110 mL/hour. Parenteral nutrition (Answer A) is inappropriate because there is no evidence that the patient's GI tract is nonfunctional. Albumin 5% (Answer B) or lactated Ringer solution (Answer D) should be reserved for fluid resuscitation in patients with signs or symptoms of intravascular volume depletion.

3. Answer: B

Although this patient has symptomatic hyponatremia, she also has signs of intravascular volume depletion. This intravascular volume depletion is a potent stimulus for ADH secretion, which will potentiate hyponatremia. In patients with hyponatremia and intravascular volume depletion, it is important to restore intravascular volume first to prevent organ hypoperfusion and to inhibit ADH secretion. Fluid resuscitation should be accomplished with 0.9% sodium chloride as a fluid bolus, followed by a reevaluation of fluid status (Answer B). A slower infusion of 0.9% sodium chloride (Answer A) will not restore intravascular volume quickly. Once the intravascular volume is restored, ADH secretion will cease. This can be followed by a water diuresis, with a subsequent rise in the serum sodium concentration. Of importance, the patient should be monitored closely to prevent a rise in serum sodium greater than 10–12 mEq/L/day. If serum sodium rises too fast, 0.45% sodium chloride can be infused to slow the rate of rise of serum sodium concentration. Hypertonic saline (Answers C and D) would not be advisable unless the patient continues to have symptoms of hyponatremia after appropriate fluid resuscitation.

4. Answer: C

To prevent central pontine myelinolysis in patients with hyponatremia, it is recommended that the serum sodium concentration be raised by no more than 10–12 mEq/L in 24 hours (Answer C). Of note, the goal is not to achieve a normal serum sodium concentration in 24 hours. Rapid correction of chronic hyponatremia can cause permanent neurologic damage (Answers A and B), and because this patient is symptomatic, she should not be maintained at her current sodium concentration (Answer D).

5. Answer: D

This patient has hyponatremia and hypokalemia. In patients with hypokalemia, there is a reduction in IC K^+. To maintain cellular electroneutrality, Na^+ will shift into cells. As K^+ is replaced, Na^+ shifts out of cells, and the serum sodium concentration rises. Therefore, in this case, the hypokalemia should be corrected first, which will cause a subsequent improvement in the hyponatremia. Because this patient has no ECG changes related to the hypokalemia, oral supplementation with K^+ (Answer D) is recommended over intravenous replacement (Answer A). A dose of 60–80 mEq/day should cause an increase in the K^+ concentration by 0.6–0.8 mEq/L. Because the patient is eating a regular diet, she should no longer require intravenous fluids (Answer B). Hypertonic saline (Answer C) is incorrect because this patient has no serious symptoms of hyponatremia.

6. Answer: D

This patient has not been given sufficient water, and she cannot communicate (or feel) thirst because of the damage from her ischemic stroke. This can be prevented by administering about 1 mL of water for every calorie administered. It should also be prevented by monitoring serum sodium concentrations and adjusting water intake as needed. To correct the hypernatremia, water should be administered, preferably through the enteral feeding tube (Answer D). If this is not possible, it can be administered intravenously as D_5W (Answer B or C), but never as sterile water (Answer A). Sterile water administered intravenously can cause hemolysis and death. The patient's water deficit (in liters) can be estimated with the equation $0.4 \times LBW \times [(Na^+/140) - 1]$. Water should be replaced over several days, taking care to avoid changes in serum sodium greater than 10–12 mEq/L in 24 hours.

7. Answer: B

Insulin (Answer B) will have the fastest onset and most predictable action of lowering serum potassium. Calcium gluconate (Answer A) should be used with caution in this patient because it can potentiate digoxin toxicity and bradycardia. The efficacy of sodium bicarbonate (Answer C) is not well established. Albuterol (Answer D) can be efficacious when added to insulin, but it might not be effective in about 40% of patients; therefore, it is not recommended as initial therapy or as monotherapy for hyperkalemia.

8. Answer: C

This patient is receiving a calorie-dense EN formula that typically has less water than other enteral products. Therefore, although not currently hypernatremic, the patient is at risk of developing hypernatremia because of insufficient water intake. This can be prevented by administering additional water. The preferred route is enteral, if possible. The additional water needed daily can be estimated as 1 mL/kcal or around 30 mL/kg/day. Therefore, if this patient is receiving enteral feeding at 35 mL/hour × 2 kcal/mL, she is receiving 1680 kcal/day. She is receiving only 717 mL of water per liter of enteral formula, which is 602 mL/day for the 840 mL of enteral feeding daily (35 mL/hour × 24 hours = 840 mL/day). Because she is receiving 1680 kcal, she needs about 1680 mL of water per day. Subtracting the water from the feedings from the total needed, 1680 − 602 = 1078 mL is needed. This can be divided and administered through the gastric feeding tube at about 180 mL/dose every 4 hours (Answer C). Of note, the patient should be monitored for fluid overload, especially given her chronic kidney disease. Given this patient's stable kidney disease and her adequate urine output, she should be able to tolerate this amount of free water. The amount of free water needed daily is an estimation that should be adjusted on the basis of specific patient parameters (e.g., serum sodium, input, output, daily weight, edema). Free water should not be administered as intravenous dextrose (Answer B) unless enteral administration is not feasible. Answer A is incorrect because reducing Na^+ will not prevent hypernatremia; the problem is related to too little water rather than too much Na^+. Answer D is incorrect because the caloric goals should not be sacrificed, and they would not eliminate the problem of insufficient water administered.

9. Answer: D

This patient is developing a respiratory acidosis, possibly because of overfeeding. Although dextrose is metabolized to water and CO_2, it generally will not cause a respiratory acidosis unless the patient is being overfed. Reducing the total calories to 25 kcal/kg decreases the risk of overfeeding, and reintubation can be avoided (Answer D). Answer A is incorrect because patients can be overfed with PN or EN. Answer B is incorrect because, even if the dextrose in the PN is reduced, the patient can still develop symptoms of overfeeding. Answer C is incorrect because the underlying (overfeeding) cause should be corrected, rather than adjusting the acetate to treat a respiratory acidosis.

10. Answer: D

To determine the amount of calories provided by propofol, it must first be determined how many milliliters per day are infused. For this patient receiving propofol 45 mcg/kg/minute and weighing 70 kg, 454 mL is infused daily (assuming a constant infusion rate). Next, if a 10% lipid emulsion provides about 1.1 kcal/mL, it can be calculated that 454 mL/day of propofol provides about 500 kcal/day, making Answer D correct and Answers A–C incorrect.

11. Answer: C

This patient has developed a metabolic alkalosis, probably secondary to the loss of gastric fluid through NG suctioning. The low serum chloride and elevated serum bicarbonate concentrations support this theory.

In addition, the acid base is consistent with metabolic alkalosis with compensatory respiratory acidosis. The treatment in this circumstance is to replace the lost fluid with 0.9% sodium chloride, which is being done. In addition, Na^+ and K^+ can be administered as the chloride salt rather than the acetate salt (Answer C). For this case, only Na^+ is converted to chloride salt, and K^+ is left as the acetate salt initially. With daily monitoring, the ratio of Cl^- to acetate can be adjusted further if needed. Answer B is incorrect because it would probably worsen the metabolic alkalosis as the sodium acetate is converted to bicarbonate. Answer A is incorrect because hypercapnia is a compensatory response, not the primary acid-base disturbance. Answer D is incorrect for several reasons. First, it is never advisable to add sodium bicarbonate to PN because of incompatibility and the risk of calcium-phosphate precipitation. Second, sodium bicarbonate is the incorrect treatment for metabolic alkalosis because it can worsen alkalosis.

12. Answer: B

The total calories are calculated by adding the calories provided by dextrose, lipid, and AA. Dextrose provides 714 kcal (210 g × 3.4 kcal/g), lipid provides about 300 kcal (30 g × 10 kcal/g), and AA provides 300 kcal (75 g × 4 kcal/g). Adding these together provides calories of 1314 kcal/50 kg = 26.3 kcal/kg, making Answer B correct and Answers A, C, and D incorrect.

13. Answer: D

This patient's hyperglycemia could be attributable to either stress or corticosteroids. Because the corticosteroid dose is being tapered, the blood glucose concentrations will probably decrease with time. For patients with a fluctuating blood glucose concentration, it can be difficult to add insulin to PN because insulin cannot be adjusted in a timely manner. Regardless, Answer A is incorrect because long-acting insulin should not be added to PN. If insulin is added to PN, it should be regular insulin. Although some experts promote "permissive underfeeding," Answer B is incorrect because it would provide insufficient calories for this patient. Sliding scales of insulin can be useful when used in conjunction with a basal amount of insulin in patients with a fluctuating blood glucose concentration. However, a sliding scale (Answer C) should not be used as the primary intervention for blood glucose control, because it is reactive and it fails to prevent hyperglycemia. In addition, the sliding scale described recommends insulin only when the blood glucose reaches 200, which is too high. Answer D is correct because it provides a basal amount of insulin that can be adjusted in a timely manner as the blood glucose concentrations fluctuate according to the patient's status.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: D

This patient continues to have hypotension and tachycardia, both of which are signs of intravascular volume depletion. The improvement in blood pressure and tachycardia after a fluid bolus also indicates intravascular volume depletion. Fluid administration should continue until there is no further improvement in vital signs. Patients with intravascular volume depletion require a rapid bolus of crystalloid (either 0.9% sodium chloride or lactated Ringer solution) of 500–1000 mL (or about 30 mL/kg), followed by reassessment (Answer D). A rapid bolus is essential to prevent organ dysfunction caused by hypoperfusion. Although the patient has poor urine output, administering furosemide (Answer A) will worsen volume depletion. As volume is replaced, urine output will probably increase. Administering 5% albumin in combination with a vasopressor (Answer B) should not be the initial treatment as long as vital signs are improving with the administration of fluid boluses with 0.9% sodium chloride. In addition, colloids are more expensive, and there is no evidence of better outcomes for fluid resuscitation with colloids than with crystalloids. Furthermore, infusion of albumin over 4 hours is incorrect because it would not restore intravascular volume rapidly enough to prevent organ dysfunction. Intravenous fluid containing D_5W (Answer C) is not appropriate for fluid resuscitation, regardless of the blood glucose concentration.

2. Answer: A

To answer this question, an alligation must first be set up using 0.9% and 23.4% sodium chloride. If 0.9% sodium chloride contains 154 mEq/L, 2% should contain about 342 mEq/L. After completing the alligation, the correct amounts can be double-checked by verifying the amount of sodium chloride in the prepared product: 951 mL of 0.9% sodium chloride contains 146 mEq of sodium chloride, and 49 mL of 23.4% sodium chloride contains 196 mEq of sodium chloride; therefore, 146 mEq + 196 mEq = 342 mEq/L of sodium chloride in the final product. The osmolarity is calculated as (2 g/100 mL) × (1 mol/58.5 g) × (2 Osm/mol) × (1000 mOsm/Osm) × (1000 mL/L) × 0.93 = 635 mOsm/L (Answer A is correct; Answer D is incorrect). Because of the osmotic coefficient (0.93), the sodium chloride does not completely dissociate in solution. Although use of the osmotic coefficient provides a more accurate osmolarity, it is probably not clinically relevant in calculating the osmolarity of intravenous sodium chloride. Therefore, it is safe to estimate the osmolarity of sodium chloride as either 635 or 684 mOsm/L, because there is no apparent clinical difference between these osmolarities. Because the osmolarity is less than 900 mOsm/L, the infusion can be administered through a peripheral line, (Answers B and C are incorrect).

3. Answer: D

In this case, hyponatremia is likely because of congestive heart failure and has probably developed over a prolonged period (not acute onset). Patients with chronic hyponatremia because of heart failure are typically asymptomatic. Rapid correction of chronic hyponatremia is associated with permanent neurologic damage caused by central pontine myelinolysis. Furthermore, hypertonic saline can worsen volume overload in patients with heart failure. Although hyponatremia is a sign of worsening heart failure, correction of hyponatremia in patients with heart failure does not improve outcomes (Answer D). For these reasons, the risks of correcting the serum sodium with hypertonic saline (Answers A–C) outweigh the potential benefits.

4. Answer: B

Patients with hyperkalemia and ECG changes should be treated first with Ca^{2+} for cardiac stability (Answer B). After Ca^{2+} administration, other measures can be taken to shift K^+ from the EC compartment to the IC compartment. Insulin (Answer A) can accomplish this; however, in this patient with hyperglycemia, insulin should be administered without glucose. Sodium polystyrene sulfonate (Kayexalate; Answer C) can be administered, but it is not effective immediately and is therefore not appropriate for first-line treatment of symptomatic hyperkalemia. Sodium bicarbonate (Answer D) is incorrect because it is not immediately effective and not an appropriate first-line option for symptomatic hyperkalemia.

5. Answer: C

This patient is not receiving adequate nutritional intake because of her mental status. Because her GI tract is functional, it should be used for feeding to prevent gut mucosal atrophy. An NG or nasoduodenal feeding tube is appropriate for enteral access for short-term

nutritional support (Answer C). A percutaneous gastrostomy tube (Answer D), which requires a surgical procedure, is used for long-term nutritional support. The patient should receive 25–35 kcal/kg/day; the caloric content in Answer D is also above the recommended range of 25–35 kcal/kg/day in this patient. The PN formulas (Answers A and B) should not be used in a patient with a functional GI tract. Although Answer B would be an appropriate PN formula for peripheral administration, PN is associated with more complications than EN is.

6. Answer: C

This correct formula provides about 30 kcal/kg of calories, 1.5 g of protein per kilogram (AA), and 30% of total calories as lipid (Answer C). Answer A is incorrect because it provides 1000 calories as lipid, which is about 62% of the total calories provided. Answer B is incorrect because it contains only 0.8 g/kg of AA, which is an insufficient amount considering the patient's stress and apparent absence of kidney injury. Answer D is incorrect because it contains too much AA.

7. Answer: B

This patient has hypomagnesemia and hypokalemia. Correction of hypokalemia requires correction of hypomagnesemia to prevent renal loss of K^+ (Answer B). Magnesium should be administered slowly to avoid hypotension and increased renal excretion caused by rapid administration. Continued K^+ should not be given until magnesium is administered (Answers A and C). Calcium correction will not have a large effect on K^+ correction (Answer D).

8. Answer: C

Enteral nutrition prevents gut mucosal atrophy and subsequent bacterial translocation (Answer C). Bacterial translocation is the crossing of bacteria from the GI tract into the systemic circulation. Enteral nutrition is associated with fewer infectious complications than PN, which may partly be because of a reduction in bacterial translocation (Answers A and B). Zinc does not affect atrophy and bacterial translocation (Answer D).

9. Answer: C

It is a common misconception that all patients with kidney failure need protein restriction (Answers A and B). This is true for chronic kidney disease patients who are not undergoing dialysis. Conversely, if they are undergoing dialysis, they do not need protein restriction and can receive AA at 1.2–1.5 g/kg/day (Answer C). Answer D is incorrect because too much protein is given.

Psychiatry and Mental Health

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Learning Objectives

1. Choose pharmacotherapeutic options for managing schizophrenia, major depressive disorder (MDD), bipolar disorder, anxiety and anxiety-like disorders, insomnia, and substance use disorders (SUDs).
2. Select a drug used to treat these disorders on the basis of its unique pharmacologic properties, therapeutic efficacy, adverse effects, and cognitive and behavioral effects.
3. Formulate a pharmacotherapeutic treatment plan for a patient with a diagnosis of schizophrenia, MDD, bipolar disorder, anxiety and anxiety-like disorders, insomnia, or SUD.

Abbreviations in This Chapter

ANC	Absolute neutrophil count
APA	American Psychiatric Association
BEN	Benign ethnic neutropenia
CANMAT	Canadian Network for Mood and Anxiety Treatments
CBT	Cognitive behavioral therapy
CIWA-Ar	Clinical Institute Withdrawal Assessment for Alcohol scale
CNS	Central nervous system
CYP	Cytochrome P450 enzyme system
DSM-5-TR	*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision*
EPS	Extrapyramidal symptoms
FGA	First-generation antipsychotic
GABA	γ-Aminobutyric acid
GAD	Generalized anxiety disorder
HAM-D/ HDRS	Hamilton Depression Rating Scale
ISBD	International Society for Bipolar Disorders
LAI	Long-acting injectable
MAOI	Monoamine oxidase inhibitor
MDD	Major depressive disorder
NMS	Neuroleptic malignant syndrome
OCD	Obsessive-compulsive disorder
OH	Orthostatic hypotension
OUD	Opioid use disorder
PANSS	Positive and Negative Syndrome Scale
PHQ-9	Patient Health Questionnaire-9
PTSD	Posttraumatic stress disorder
REM	Rapid eye movement
REMS	Risk Evaluation and Mitigation Strategies
SAMHSA	Substance Abuse and Mental Health Services Administration
SGA	Second-generation antipsychotic
SNRI	Serotonin-norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
SUD	Substance use disorder
TCA	Tricyclic antidepressant

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

1. A 36-year-old presents with a 16-year history of schizophrenia and alcohol use disorder. Medication was recently changed from haloperidol to aripiprazole because of gynecomastia and sexual dysfunction. Today, the patient is pacing in your office and seems anxious and agitated. The patient has not been sleeping well and feels uncomfortable in their skin. Which medication would be most appropriate to help relieve this patient's symptoms?
   A. Benztropine.
   B. Dantrolene.
   C. Lorazepam.
   D. Propranolol.

2. A 52-year-old (current BMI 35 kg/m^2) with schizophrenia presents for a routine follow-up. Abnormal, uncontrollable repetitive chewing-type movements in their jaw exist. These movements are bothersome and interfere with eating ability. The patient stays home because of shame about being seen in public. Medication history includes perphenazine for the past 8 years with good control of symptoms. The patient is able to live independently and care for themselves. Therapeutic trials of aripiprazole, ziprasidone, and haloperidol have yielded subtherapeutic results. A 22.7-kg (50 lb) weight gain and development of type 2 diabetes occurred while taking olanzapine. The diabetes resolved off olanzapine. Which would be the best treatment?
   A. Add benztropine.
   B. Add lorazepam.
   C. Change to quetiapine.
   D. Add valbenazine.

3. A 67-year-old is admitted for new-onset tonic-clonic seizures. Medical history is negative for seizure disorders but positive for prediabetes and schizophrenia. The patient has long-term, stable schizophrenia controlled with clozapine 900 mg daily. Additional medications include diphenhydramine 50 mg at bedtime, metformin 1000 mg twice daily, and bupropion extended release (ER) 300 mg daily (for 2 months). Social history is negative for alcohol and illicit drug use but positive for a 25 pack-year tobacco history, which was stopped 2 weeks ago. Which medication is most likely responsible for the seizures?
   A. Bupropion.
   B. Clozapine.
   C. Diphenhydramine.
   D. Metformin.

4. A 25-year-old presents to your practice with a depressed mood that has worsened during the past few weeks. The patient finds it difficult to get out of bed in the morning. When not sleeping, the patient is eating. Weight has increased by 4.5 kg (10 lb) in the past month. They are worried about their job and do not feel that they are "pulling [their] weight," even though they recently received a glowing evaluation. They have passive thoughts of harming themselves but no definite plan. Medical history includes anxiety, gastroesophageal reflux disease, and hypothyroidism thyrotropin within normal limits). Current medications include levothyroxine 100 mcg daily, lansoprazole 30 mg every morning, and alprazolam 0.5 mg three times daily for anxiety. Which medication would best treat the current symptoms?
   A. Desipramine.
   B. Fluoxetine.
   C. Mirtazapine.
   D. Paroxetine.

5. A 56-year-old presents with a medical history significant for recurrent major depression and type 2 diabetes with newly diagnosed neuropathy, obesity, and coronary artery disease. Current medications include citalopram 40 mg daily, carvedilol 25 mg twice daily, lisinopril 40 mg daily, and metformin 1000 mg twice daily. The patient is tearful during the appointment and continues to have symptoms of depression despite initial improvement with citalopram. The patient wants to change antidepressants. Which would be most beneficial?
   A. Bupropion.
   B. Duloxetine.
   C. Nortriptyline.
   D. Sertraline.

6. A 45-year-old presents with agitation and diaphoresis and an oral temperature of 38.5°C (101.3°F). Their right eyelid began twitching about an hour ago, and it will not stop. Cold symptoms developed 2 days ago, and the patient began taking dextromethorphan and pseudoephedrine around-the-clock. Medical history includes depression, hypertension, and dyslipidemia. Current medications include cetirizine 10 mg at bedtime, paroxetine 40 mg at bedtime, diltiazem extended release (XR) 240 mg daily, and rosuvastatin 10 mg daily. Which combination of medications is most likely contributing to the current symptoms?
   A. Cetirizine and paroxetine.
   B. Dextromethorphan and pseudoephedrine.
   C. Diltiazem and pseudoephedrine.
   D. Paroxetine and dextromethorphan.

7. A 31-year-old presents with a 5-year history of type I bipolar disorder, which is treated with lithium 300 mg twice daily. The patient has been adherent to treatment. A lithium serum concentration, obtained yesterday before the morning lithium dose, is 1.0 mEq/L. There have been no manic symptoms for the past few years. Current admission is for a suicide attempt using acetaminophen. For the past few weeks, they have lost interest in their job and isolated themselves from other people. Which medication would best help the acute symptoms?
   A. Aripiprazole.
   B. Lamotrigine.
   C. Quetiapine.
   D. Venlafaxine.

8. A 28-year-old woman (height 61 inches, weight 74.8 kg, up from 68 kg 2 months ago) presents with a history of type I bipolar disorder. She has taken lithium 450 mg twice daily for the past 6 months. Her last lithium serum concentration (3 months ago) was 0.7 mEq/L. She presents today for an annual examination. Her laboratory test results include sodium 138 mEq/L, potassium 4.7 mEq/L, serum creatinine 0.9 mg/dL, glucose 124 mg/dL, and thyrotropin 24 mIU/mL. Additional medications include olanzapine 10 mg at bedtime (for 1 year), ethinyl estradiol/drospirenone daily, and a multivitamin. Which laboratory finding is most closely associated with her current medication regimen?
   A. Glucose.
   B. Serum creatinine.
   C. Sodium.
   D. Thyrotropin.

9. A 43-year-old presents with right upper quadrant abdominal pain with rebound tenderness, nausea, and vomiting. Medical history is significant for rapid-cycling bipolar disorder, hypertension, obesity, and asthma. Current medications include divalproex sodium 500 mg twice daily, lamotrigine 150 mg twice daily, aripiprazole 30 mg daily, ramipril 10 mg daily, albuterol hydrofluoroalkane (HFA) 2 puffs every 6 hours, and fluticasone/salmeterol dry powder inhaler 250/50 mcg twice daily. A prednisone taper was initiated 3 days ago for an asthma exacerbation. Laboratory test results include sodium 141 mEq/L, potassium 3.3 mEq/L, chloride 95 mEq/L, carbon dioxide 26 mmol/L, serum creatinine 1.0 mg/dL, glucose 72 mg/dL, total cholesterol 165 mg/dL, triglycerides 188 mg/dL, aspartate aminotransferase (AST) 27 U/L, alanine aminotransferase (ALT) 21 U/L, amylase 456 U/L, lipase 387 U/L, and valproic acid trough concentration 56 mg/dL. Which medication is most likely to be impacted with her current medication regimen?
   A. Aripiprazole.
   B. Divalproex sodium.
   C. Lamotrigine.
   D. Prednisone.

10. A 20-year-old presents to the emergency department after experiencing trembling, sweating, chest pain, and shortness of breath accompanied by intense fear. A myocardial infarction has been ruled out. The patient is diagnosed with panic disorder. In addition to a medication for acute symptoms, which medication would provide the best long-term control?
   A. Alprazolam.
   B. Buspirone.
   C. Hydroxyzine.
   D. Paroxetine.

11. A 55-year-old woman presents with uncontrolled generalized anxiety disorder (GAD). Concomitant medical conditions include a history of breast cancer, dyslipidemia, osteoarthritis, vasomotor symptoms, and osteopenia. She takes tamoxifen, simvastatin, ibuprofen, lorazepam, and alendronate. Her physician would like her to have better control of her anxiety symptoms. He would also like to taper off lorazepam. Her GAD has not been controlled with escitalopram, sertraline, or duloxetine. Which agent would be best?
   A. Bupropion.
   B. Fluoxetine.
   C. Pregabalin.
   D. Venlafaxine.

12. A 74-year-old has difficulty getting to sleep. Once asleep, rest is comfortable throughout the night. The patient has struggled with keeping a consistent bedtime for the past few months. There are no identifiable contributing factors. Concomitant medical conditions include hypertension, arthritis, and mild cognitive impairment. Diphenhydramine helped for only a few nights and "made me loopy." They would like a medication with the least risk of hangover effect. Which medication is best?
   A. Eszopiclone.
   B. Ramelteon.
   C. Suvorexant.
   D. Zolpidem.

13. A 23-year-old has a history of heroin addiction and has successfully been maintained on methadone 40 mg daily for 1 year. The patient would like an option that does not require a visit to a daily opioid treatment program to get their methadone dose. The patient is taking no other medications or substances of abuse. Which treatment regimen is most appropriate?
    A. Initiate supervised buprenorphine/naloxone.
    B. Change to buprenorphine × 2 days; then take buprenorphine/naloxone.
    C. Change to naltrexone.
    D. Taper to methadone 30 mg; then change to buprenorphine.

14. A 55-year-old has a 30-year history of alcohol dependence. Daily intake is 1 pint of vodka. Several quit attempts have been unsuccessful. They recently reconciled with their estranged son and want to be sober so that they can be present in their son's life. Medical history includes heroin use, depression, and posttraumatic stress disorder (PTSD). Concomitant medications include methadone maintenance (which they wish to continue) and sertraline (currently nonadherent). Liver function test results include AST 143 U/L, ALT 74 U/L, albumin 4.0 g/dL, alkaline phosphatase 75 U/L, total bilirubin 0.3 mg/dL, prothrombin time 15.1 seconds, international normalized ratio (INR) 0.9, platelet count 370,000/mm^3, and creatinine clearance 40 mL/minute/1.73 m^2. After alcohol detoxification, which maintenance treatment is most appropriate?
    A. Acamprosate 333 mg three times daily.
    B. Chlordiazepoxide 25 mg four times daily.
    C. Disulfiram 500 mg daily.
    D. Naltrexone 50 mg daily.

15. A 44-year-old is preparing to be discharged from the hospital after a myocardial infarction. They have a 25 pack-year history of smoking cigarettes and currently smokes 1½ packs/day. Two unsuccessful quit attempts exist, including quitting "cold turkey" the first time about 5 years ago. Smoking resumed 6 months later after a job loss. Another attempt occurred 6 months ago using the 2-mg strength of nicotine gum. Seven pieces were chewed daily in an effort to save money. The patient has just been given a diagnosis of depression. Which regimen would be best?
    A. Bupropion sustained release (SR).
    B. Nicotine gum.
    C. Nicotine patch.
    D. Varenicline.

BPS Pharmacotherapy Specialty Examination Content Outline

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline, tested during the Spring 2024 window:

1. Patient-Centered Pharmacotherapy
    a. 1.1. Develop patient-centered, evidence-based pharmacotherapy plans. Subtasks: 1.1.1–1.1.17
    b. 1.2. Monitor the patient to ensure safe and effective pharmacotherapy. Subtasks: 1.2.1–1.2.4
    c. 1.3. Modify pharmacotherapy plans through ongoing patient assessment. Subtasks: 1.3.3–1.3.7

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline, tested starting Fall 2024:

1. Patient Care Specialty Areas
    a. 1B. Secondary Pharmacotherapy Specialty Areas. Subtask: 1B7
2. Therapeutics and Patient Management
    a. 2A. Treatment Planning. Subtasks: 2A1–2A6
    b. 2B. Therapeutic Implementation. Subtasks: 2B1, 2B2
    c. 2C. Treatment Outcomes and Monitoring. Subtasks: 2C1–2C5
3. Professional Practice
    a. 3A. Quality of Care. Subtasks: 3A1–3A4
    b. 3C. Practice Management. Subtask: 3C1

Patient Case

Questions 1–4 pertain to the following case.

A 25-year-old (BMI 35 kg/m^2) has recently diagnosed schizophrenia. The patient often hears voices telling them they are "stupid and worthless" and should "just jump off the roof of their apartment building." The patient's parents became very concerned about isolative behavior and brought the patient to the hospital. The patient was given haloperidol in the psychiatry unit and now presents with neck stiffness and in oculogyric crisis. Until now, they have not taken medications because they thought they could control their symptoms on their own with vitamins, though they have difficulty remembering to take these. The patient has an additional history of marijuana and alcohol use disorders. A blood alcohol concentration is 0, and a urine drug screen is negative.

1. Which is most appropriate for this patient's symptoms at this time?
   A. Benztropine.
   B. Dantrolene.
   C. Lorazepam.
   D. Propranolol.

2. Aripiprazole is initiated. Which is the best rationale for this selection, given patient-specific factors?
   A. Aripiprazole has no risk of causing extrapyramidal symptoms (EPS).
   B. Aripiprazole is available in a long-acting injection (LAI) to increase adherence.
   C. Aripiprazole would eliminate this patient's negative symptoms.
   D. Aripiprazole is effective against substance use disorders.

3. Which is the best example of an adverse effect of aripiprazole that would be of concern when initiated in this patient?
   A. Sedation.
   B. Anticholinergic effects.
   C. Akathisia.
   D. Corrected QT (QTc) prolongation.

4. One year later, they no longer respond to aripiprazole, and you decide to change their medication. They are only interested in oral medications. Given this patient's history, which agent is most appropriate at this time?
   A. Clozapine.
   B. Fluphenazine.
   C. Olanzapine.
   D. Ziprasidone.

I. SCHIZOPHRENIA

A. Characteristics

1. Schizophrenia is a disorder involving psychosis and a complex mix of symptoms. The *Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition, Text Revision* (*DSM-5-TR*) identifies five symptoms for diagnosis. At least two of the following symptoms must be present for at least 1 month, and at least one of the symptoms should be delusions, hallucinations, or disorganized speech. Continuous signs of disturbance must be present for at least 6 months.

a. Delusions: Fixed false beliefs involving misinterpretations of reality that are resistant to evidence refuting them. Trying to dispel a delusion can undermine therapeutic alliance. Examples include persecutory (e.g., someone is going to get me), paranoid (e.g., someone is watching), and command (e.g., someone told me to do it).
b. Hallucinations: Perceptual abnormalities that can involve any sensory system. Auditory hallucinations are the most common.
c. Disorganized speech: This manifests as frequent "derailment" of speech or incoherence.
    i. "Loose associations": Going from one unrelated topic to another as though the topics were connected
    ii. "Tangential" speech refers to answers to questions that are only slightly related or that are totally unrelated to the question.
    iii. "Word salad" refers to speech that is almost incomprehensible and is very much like receptive aphasia.
d. Grossly disorganized or catatonic behavior
e. Negative symptoms (Table 1)

2. Schizophrenia can be divided into positive, negative, and cognitive symptoms (see Table 1).
3. Anosognosia: Many patients (57%–98%) with schizophrenia may lack awareness of or insight into their illness, particularly during an acute episode. Anosognosia may or may not improve with treatment. It is the most common predictor of nonadherence and predicts higher relapse rates, more involuntary treatments, poorer psychosocial functioning, aggression, and a poorer course of illness.

Table 1. Categories of Schizophrenia-Associated Signs and Symptoms

Positive (presence of something that should not be there)	**Negative (absence of something that should be present)**	**Cognitive**
Antipsychotics are most effective	**Antipsychotics may not be completely effective**	**No current medications effectively treat**
Hallucinations[a]	Blunted or flat affect[a]	Poor executive function
Delusions[a]	Social withdrawal (passive-apathetic)[a]	Impaired attention
Paranoia or suspiciousness[a]	Lack of personal hygiene	Impaired working memory (does not learn from mistakes)
Conceptual disorganization[a,b]	Prolonged time to respond[a]	
Hostility[a]	Poor rapport[a]	
Grandiosity[a]	Poor abstract thinking[a]	
Excitement[a]	Poverty of speech (lack of spontaneity and flow of conversation)[a]	
Loose associations	Emotional withdrawal[a]	
Thought broadcasting	Alogia (poverty of speech)	
Thought insertion	Ambivalence (simultaneous, contradictory thinking); prevents decision-making	
	Asociality; internally directed	
	Amotivation (avolition)	
	Anhedonia	

[a]These symptoms are used to score the positive and negative portions of the Positive and Negative Syndrome Scale (PANSS).

[b]Conceptual disorganization, according to the Brief Psychiatric Rating Scale (BPRS), is the "degree to which speech is confused, disconnected, vague or disorganized." This includes tangential thinking, circumstantiality, sudden topic shifts, incoherence, derailment, blocking, neologisms, clanging, word salad, and other speech disorders.

B. Course of Illness
   1. Onset is usually between adolescence and early adulthood. Schizophrenia occurs earlier in men (i.e., early 20s) than in women (i.e., late 20s to early 30s). The prevalence is around 1.1% and is equal between the sexes.
   2. Some patients fluctuate between acute episodes and decreased presence or absence of positive symptoms. Residual symptoms are often present between episodes.
   3. The lifetime course of schizophrenia has four phases: prodromal, acute, stabilization, and stable.
      a. Prodromal: Characterized by the gradual development of symptoms that may go unnoticed until a major positive symptom occurs. This phase may include isolation, deterioration of hygiene, loss of interest in work or school, and dysphoria.
      b. Acute: Clinically significant positive symptoms are present, often requiring hospitalization. Patients may be unable to care for themselves during this phase.
      c. Stabilization: The acute symptoms begin to decrease, and this phase may last for several months.
      d. Stable: During this phase, positive symptoms have markedly declined and may not be present. Negative symptoms may resolve. Cognitive symptoms may be present. Nonpsychotic symptoms such as anxiety and depression may be present.
   4. Complete remission without symptoms is uncommon.

C. Causes
   1. The causes of schizophrenia are unknown. Schizophrenia appears to involve neurophysiologic and psychological abnormalities.
   2. The primary neurotransmitters believed to be involved are dopamine and serotonin. The exact relationship between these neurotransmitters remains unknown. In some areas of the brain, dopamine overactivity appears to result in some symptoms, whereas in others, underactivity may occur. Glutamatergic receptor dysfunction may also play a role in causing schizophrenia. Glutamate is associated with several processes that involve cognition, memory, and perception.
   3. Schizophrenia is likely a constellation of disorders rather than one distinct disorder. It likely results from a combination of genetics and environment. Many potential risk factors for schizophrenia have been identified, including a family history of schizophrenia, perinatal trauma (e.g., hypoxia, fetal distress, influenza, and nutritional deficiencies), obstetric complications, living in an urban area, having stress, and being born during the winter.

D. Rating Scales
   1. The Brief Psychiatric Rating Scale (BPRS), developed in 1962, is a general psychiatric rating scale that has been used to measure outcomes in clinical trials, including those involving schizophrenia.
   2. The Positive and Negative Syndrome Scale (PANSS) is a 30-item, 7-point scale that was partly adapted from the BPRS. Lower scores mean fewer symptoms. The PANSS is considered the gold standard and is widely used to evaluate antipsychotic therapy in clinical trials but not in daily clinical practice. This scale requires a 45-minute interview with the patient. The interviewer must be specially trained to administer it.
   3. The PANSS-6 is a scalable abbreviated version of the PANSS that can be used clinically. It consists of the following components: delusions, conceptual disorganization, hallucinations, blunted affect, social withdrawal, and lack of spontaneity and flow of conversation. It is sensitive to changes in treatment. A score of less than 14 signifies remission (out of 42).

E. Antipsychotics
   1. First-line agents for treating schizophrenia
   2. Two classes

a. First-generation antipsychotics (FGAs; also called typical or conventional antipsychotics; Table 2). These include all the older antipsychotics. Chlorpromazine, a phenothiazine, was the first to be used clinically.

Table 2. First-Generation Antipsychotics for Schizophrenia

Agent	Dose Equivalent (mg)	Potency[a]	Anticholinergic	Sedation	Orthostatic Hypotension	Extrapyramidal Symptoms
Chlorpromazine (Thorazine)[b]	100	Low	+++	++++	+++	++
Fluphenazine (Prolixin)[b]	2	High	+	+	+	+++
Haloperidol (Haldol)	2	High	+	+	+	+++
Loxapine (Adasuve, Loxitane)	10	Int.	++	++	++	++
Molindone (Moban)	—	—	+	++	+	++
Perphenazine (Trilafon)[b]	10	Int.	++	++	++	++
Pimozide (Orap)	2	High	+	+	+	+++
Thioridazine (Mellaril)[b]	100	Low	+++	+++	+++	+
Thiothixene (Navane)	4	High	+	+	+	+++
Trifluoperazine (Stelazine)[b]	5	Int	++	+	+	++

[a]Potency = D_2 receptor affinity.

[b]Phenothiazine.

Int. = intermediate.

i. These agents can be categorized according to potency as antagonists at the dopamine D_2 receptors, which are thought to be the mechanism of pharmacologic activity, particularly in the mesolimbic areas of the brain for treating psychotic symptoms. Blockade in the mesocortical areas may worsen negative and cognitive symptoms. Potency at the D_2 receptors can be split into low, intermediate, and high. FGAs can be interconverted using chlorpromazine dose equivalents.

ii. Adverse effect profiles also differ by potency and are relatively uniform for agents with similar dopamine potency.

(a) Low potency: Concomitant anticholinergic, antihistaminic, and α-adrenergic blocking properties are also present.

(b) High potency: Less potency at the other receptors; dopamine-related adverse effects, including extrapyramidal symptoms (EPS) and hyperprolactinemia, tend to be the main adverse effects and are more prevalent than with low-potency agents.

(c) Sedation: More common with low-potency agents. Sedation is usually worse initially and then better tolerated with time. Sedation tends to be dose related.

(d) Anticholinergic effects: More common with low-potency agents. Dry mouth, constipation, blurred vision, and urinary hesitancy can occur. Dose-dependent.

(e) Orthostatic hypotension (OH): More common with low-potency agents because of blockade of the α-adrenergic receptor.

b. Second-generation antipsychotics (SGAs; also called atypical antipsychotics; see Table 3): These include the newer agents, beginning with clozapine. The adverse effect profile of SGAs is more heterogeneous and differs from that of FGAs.

Table 3. Second-Generation Antipsychotics for Schizophrenia

Drug (generic/ brand)	Metabolic Syndrome			Anticholinergic	Sedation	Orthostasis	Extrapyramidal Symptoms	
	Weight Gain	Glucose Abnormality	Dyslipidemia				Akathisia	Parkinsonism
Aripiprazole (Abilify)	+	+	+	+	+	+	++	+
Asenapine (Saphris)	++	++	++	+	++	++	++	+
Brexpiprazole (Rexulti)	+	+	++	+	++	+	++	+
Cariprazine (Vraylar)	++	+	+	++	++	++	++	+
Clozapine (Clozaril)	+++	+++	+++	+++	+++	+++	+	+
Iloperidone (Fanapt)	++	++	+	+	+	+++	+	+
Lumateperone (Caplyta)	+	-	-	+	+	+	-	-
Lurasidone (Latuda)	+	++	++	+	+	+	++	++
Olanzapine (Zyprexa)	+++	+++	+++	++	++	++	++	++
Paliperidone (Invega)	++	+	++	+	+	++	++	++
Quetiapine (Seroquel)	++	++	+++	++	+++	++	+	+
Risperidone (Risperdal)	++	++	+	+	++	++	++	++
Ziprasidone (Geodon)	+	+	+	+	++	++	++	+

i. SGAs were developed to reduce EPS adverse effects, including tardive dyskinesia, and to improve efficacy. The characteristics that define "atypicality" are not all agreed on, but in general, they all share at least three characteristics:
   (a) The risk of EPS is lower than with typical antipsychotics at usual clinical doses,
   (b) The risk of tardive dyskinesia is reduced, and
   (c) The ability to block serotonin-2A receptors is present. This third property may improve the negative symptoms of schizophrenia and reduce the risk of EPS. This may also be related to SGA efficacy in mood disorders.

ii. Some unique mechanisms exist among individual SGAs that may influence the effects on symptoms of schizophrenia:
   (a) Some low-potency SGAs, including quetiapine and clozapine, have faster dissociation/ weaker affinity binding at D_2 receptors.
   (b) Some SGAs have partial agonism at D_2 receptors (aripiprazole, brexpiprazole, cariprazine). This may stabilize dopamine transmission by reducing D_2 hyperactivity in the mesolimbic neurons.
   (c) Cariprazine has high potency at D_3 receptors, with may confer some benefit against negative and cognitive symptoms.

(d) Many SGAs have partial activity at serotonin-1A receptors. This may increase the release of dopamine in the prefrontal cortex, which may benefit cognition. It may also decrease EPS and improve mood. Clozapine, quetiapine, and ziprasidone have some serotonin-1A activity, but aripiprazole, brexpiprazole, and cariprazine appear to have more potent activity.

iii. Many clinicians see SGAs as first-line agents, likely because of the decreased risk of EPS. SGAs (particularly clozapine and olanzapine) have been associated with new-onset diabetes and metabolic syndrome. All patients prescribed SGAs should be monitored for BMI, blood pressure, fasting glucose, lipids, and waist circumference at baseline and periodically thereafter according to the American Psychiatric Association (APA)/American Diabetes Association (ADA) consensus recommendations.

F. Adverse Effects of Antipsychotics

1. All antipsychotics carry a boxed warning against use in older adults with dementia. FGAs may have a higher mortality rate than SGAs when used in older adults with dementia.
2. Some antipsychotics indicated for the treatment of mood disorders (particularly depression) carry a boxed warning for an increased risk of suicidal thoughts and behavior in children, adolescents, and young adults (24 years and younger) similar to antidepressants (see the Major Depressive Disorder [MDD] section in the text that follows for more details). The antipsychotics included in this warning are aripiprazole, brexpiprazole, cariprazine, lumateperone, lurasidone, and quetiapine.
3. EPS: Can occur with all antipsychotics, but are most common among the FGAs, particularly the high-potency agents. EPS are thought to result from blockade of D_2 receptors in the nigrostriatal pathway. There are four main manifestations:
   a. Pseudoparkinsonism: This is manifested by symptoms such as bradykinesia, rigidity, tremor, or akinesia. If possible, the dose of the antipsychotic should be lowered or the patient changed to another antipsychotic with less possibility of causing parkinsonism. If neither is possible, parkinsonism is usually responsive to oral anticholinergic agents such as diphenhydramine, trihexyphenidyl, and benztropine.
   b. Dystonia: These episodes are often acute. The risk is greatest in young men and with high doses of parenteral antipsychotics. Examples include torticollis, laryngospasm, and oculogyric crisis. Acute dystonia is treated with intramuscular anticholinergics. Oral anticholinergics are often used to prevent dystonias in high-risk patients.
   c. Akathisia: This is a somatic restlessness and inability to stay still or calm. Reducing the antipsychotic dose and changing to an agent with a lower incidence of akathisia are the best options, but these are not always feasible. Akathisia responds poorly to anticholinergics. Lipophilic (fat soluble) β-blockers such as propranolol are typically used. Data analyses for efficacy are inconclusive, but β-blockers are commonly used in practice. Benzodiazepines can also be used to treat akathisia but are considered second line behind β-blockers. Agents with serotonin-2 activity, including mirtazapine (which has the most evidence), trazodone, and cyproheptadine, may also be helpful.
   d. Tardive dyskinesia: Characterized by abnormal involuntary movements that occur with long-term antipsychotic therapy. Tardive dyskinesia usually involves the orofacial muscles and is often insidious. With continued drug exposure, particularly at high doses, tardive dyskinesia is often irreversible. Risks are likely related to the total cumulative dose. Those taking high antipsychotic doses, those older than 54 years, women, and those with mood disorders are also at an increased risk. Symptoms may decrease over time with lowering the antipsychotic dose (after an initial symptom increase). However, this dose reduction must be weighed against worsening symptoms of schizophrenia. Changing to an agent that is associated with less tardive dyskinesia is also an option. The risk is higher with FGAs than with SGAs. Clozapine has not been associated with tardive dyskinesia, and changing to this drug may be appropriate for patients with moderate to severe symptoms.

The other SGAs also appear to have a low potential to cause tardive dyskinesia. Patients taking antipsychotics should be monitored at least annually using a rating scale, such as AIMS (Abnormal Involuntary Movement Scale) or DISCUS (Dyskinesia Identification System Condensed User Scale).

   i. Valbenazine (Ingrezza) and deutetrabenazine (Austedo) are both U.S. Food and Drug Administration (FDA) approved for tardive dyskinesia. The exact mechanism of action is unknown, but both agents reversibly and selectively inhibit the vesicular monoamine transporter 2 (VMAT2). This transporter regulates the packaging of dopamine and other monoamines in the neuronal cytoplasm into vesicles for storage and release into synapses. Valbenazine is dosed once daily and must be adjusted for strong CYP3A4 and CYP2D6 inhibitors. Deutetrabenazine is dosed twice daily and must be adjusted for strong CYP2D6 inhibitors. Adverse effects of both include sleepiness, depression, and QTc prolongation. Deutetrabenazine carries a boxed warning regarding increased risk of suicidality. Tetrabenazine, a VMAT2 inhibitor indicated for the treatment of chorea associated with Huntington disease, is also used off-label for tardive dyskinesia.
   ii. Anticholinergic agents should not be given to treat tardive dyskinesia and may in fact worsen the symptoms.

4. Neuroleptic malignant syndrome (NMS): Can occur with all agents but is more common with high-potency FGAs. This syndrome is manifested by agitation, confusion, changing levels of consciousness, muscle rigidity, fever, tachycardia, autonomic instability, and diaphoresis. The mortality rate is high and should be treated as a medical emergency. Discontinue the offending agent and give supportive therapy, including fluids and cooling. Bromocriptine and dantrolene have been used with varying success. Do not reinitiate antipsychotics until at least 14 days after resolution of NMS symptoms.
5. Hyperprolactinemia: Antipsychotics, particularly FGAs, can block the effects of dopamine in the tuberoinfundibular pathway. This increases prolactin excretion, which can lead to breast enlargement, galactorrhea, sexual dysfunction, infertility, and menstrual changes. Among the SGAs, risperidone and paliperidone carry the highest risk of hyperprolactinemia. Aripiprazole, with its partial dopaminergic agonist activity, has been shown to lower prolactin concentrations.
6. Sexual dysfunction: Erectile dysfunction occurs in 23%–54% of men. Loss of libido and anorgasmia may occur in men and women.
7. Weight gain and diabetes: Weight gain occurs in up to 40% of patients. Diabetes can also develop, with 60% of cases occurring within the first 6 months. Among the SGAs, the risk is highest with clozapine and olanzapine, followed by quetiapine and risperidone. Among the FGAs, low-potency agents have a higher risk than high-potency agents. Important interventions include keeping the dose as low as possible and implementing dietary management to minimize weight gain. Weight gain may occur because of actions at histamine or serotonin receptors.
8. QTc prolongation: Electrocardiographic (ECG) changes occur with antipsychotics. QTc prolongation can predispose the patient to ventricular arrhythmias, including torsades de pointes. The risk of QTc prolongation appears highest with chlorpromazine, intravenous haloperidol, and thioridazine. Among the SGAs, clozapine, ziprasidone, and iloperidone appear to have the highest risk, though the other agents may cause ECG changes to a lesser extent or when combined with other agents that prolong the QTc interval. Patients must be assessed for predisposing factors such as preexisting ECG abnormalities, electrolyte disturbances, and concurrent therapy with other drugs that prolong the QTc interval. A list of medications that can prolong the QTc is available at https://www.crediblemeds.org/.
9. Seizures: Antipsychotic medications lower the seizure threshold. The risk is highest with predisposing factors such as pre-existing seizure disorder or concomitant treatment with other medications that lower the seizure threshold. Chlorpromazine, cariprazine, and clozapine carry the highest risk. Aripiprazole, fluphenazine, haloperidol, pimozide, risperidone, thioridazine, and trifluoperazine carry the lowest risk.

10. Thermoregulation: Antipsychotics are associated with poikilothermia, or difficulty regulating the body temperature. Patients should use caution when exercising or during exposure to high temperatures because hyperthermia can occur. In addition, the anticholinergic effects of antipsychotics can interfere with sweating, further compounding the problem. Patients should be educated to avoid the heat and, if they cannot, to hydrate well. Hypothermia is a risk with low temperatures. Thermoregulatory problems are more common with low-potency FGAs, but they are also possible with SGAs that have more anticholinergic properties, such as clozapine, olanzapine, and quetiapine.

G. Drug-Drug Interactions: Many antipsychotics are metabolized by the CYP system (Table 4). The presence of a CYP inducer or inhibitor may require antipsychotic dose adjustment. For example, tobacco dependence, particularly smoking, is common in patients with schizophrenia. A patient taking a CYP1A2 substrate antipsychotic who undergoes smoking cessation may require a reduced antipsychotic dose. This is particularly true of clozapine, olanzapine, and asenapine. Many SGAs metabolized by CYP2D6 and/or CYP3A4 carry dose adjustment recommendations.

Table 4. Selected Antipsychotics and the CYP System

	1A2	2D6	3A4
Substrate	Asenapine Clozapine[a] Olanzapine Ziprasidone	Aripiprazole Brexpiprazole[a] Iloperidone[a] Perphenazine Risperidone	Aripiprazole Brexpiprazole[a] Cariprazine[a] Haloperidol Iloperidone[a] Lumateperone[b] Lurasidone[a] Pimavanserin[a] Quetiapine[a] Ziprasidone
Inducer	Cannabis (smoking) Tobacco (smoking)		
Inhibitor	Caffeine (high dose)	Cannabis Chlorpromazine Fluphenazine	

[a]Dose adjustment required when used concomitantly with an inhibitor or inducer of that specific CYP enzyme.
[b]Avoid use with concomitant inducers or inhibitors.

H. FGAs for Schizophrenia: Administration Tips and Specific Agents
1. Oral tablet therapy is the most common.
2. Parenteral antipsychotics can be used acutely if patients do not adhere to therapy, are agitated and will not take oral medications, or are a danger to themselves and/or others. Several FGAs are available as parenteral injections that are given intramuscularly, including fluphenazine and chlorpromazine, but haloperidol is most commonly used. Intravenous haloperidol has been linked to cardiac toxicity, including torsades de pointes, and is not recommended.
3. Loxapine is available in an inhalable formulation for the treatment of agitation associated with schizophrenia or type I bipolar disorder. Patients should be screened for pulmonary disease. Inhalable loxapine should not be administered to patients with a history of asthma, chronic obstructive pulmonary disease, or other forms of bronchospasm. Loxapine has a Risk Evaluation and Mitigation Strategies (REMS) program associated with the bronchospasm. Health professionals must be specially trained on the Adasuve system and have supplies on hand to treat bronchospasm, including a short-acting bronchodilator such as albuterol, a nebulizer, and nebulizer solution. The most common adverse effects include dysgeusia, sedation, and throat irritation.

4. Depot forms (or long-acting injectables [LAIs]) of haloperidol and fluphenazine are available, providing sustained concentrations for about 1 month for haloperidol and 2–3 weeks for fluphenazine. LAIs are indicated as chronic therapy in patients who have benefitted from and have tolerability to oral therapy, but may have difficulty adhering to taking a daily medication, or patient preference. Both haloperidol and fluphenazine decanoate may require "bridging" (oral overlap) with oral therapy when treatment is initiated. Haloperidol decanoate can alternatively be loaded without the need for overlap with oral medication. Both haloperidol decanoate and fluphenazine decanoate contain sesame oil and thus should be avoided in patients with relevant allergies.

I. SGAs for Schizophrenia: Specific Agents
   1. Clozapine: The first "atypical" antipsychotic. Clozapine is indicated only for treatment-resistant schizophrenia (defined as lack of response to two or more adequate trials of antipsychotics, usually of different classes). Lack of response usually refers to positive symptoms, though it may also include negative symptoms. Clozapine is also indicated in patients with schizophrenia or schizoaffective disorder who have suicidal ideation. The APA endorses this indication, as well as using clozapine for patients with schizophrenia with substantial aggressive behavior despite other treatments. Clozapine is not associated with EPS or tardive dyskinesia, and it better reduces negative symptoms than FGAs.
      a. Several boxed warnings limit its use.
         i. Severe neutropenia (agranulocytosis): This is the most limiting adverse effect. Severe neutropenia can lead to a dramatic decrease in neutrophils, which increases the risk of serious or fatal infections. Severe neutropenia is defined as an absolute neutrophil count (ANC) less than 500 cells/mm^3. The incidence is about 0.9% and is highest during the first 4–6 months of therapy. Previously, both the white blood cell count and the ANC were used to monitor safety. As of 2015, only the ANC is used, and lower values are allowed for therapy. Allowances are also made for patients who have benign ethnic neutropenia (BEN; included in Table 5). Because of the severity of the neutropenia, all patients must be registered under a centrally managed REMS program (www.newclozapinerems.com), which consolidates the six previous individual programs. Prescribers and pharmacies must also be registered. Laboratory work must be submitted to the national registry before clozapine can be dispensed. Table 5 presents details of hematologic monitoring.

Table 5. Hematologic Monitoring for Clozapine

ANC Concentration	Clozapine Treatment Recommendations	ANC Monitoring
Normal range for a new patient: General population (> 1500 cells/mm^3)	Initiate treatment If treatment interrupted: < 30 days, continue monitoring as before ≥ 30 days, monitor as if new patient	Weekly from initiation to 6 mo Every 2 wk from 6 to 12 mo Monthly after 12 mo
BEN population (≥ 1000 cells/mm^3) Obtain at least two baseline ANC concentrations before initiating treatment		

Table 5. Hematologic Monitoring for Clozapine (*Cont'd*)

ANC Concentration	Clozapine Treatment Recommendations	ANC Monitoring
Mild neutropenia (1000–1499 cells/mm^3)[a]	GENERAL POPULATION Continue treatment	GENERAL POPULATION Three times weekly until ANC ≥ 1500 cells/mm^3 Once ANC ≥ 1500 cells/mm^3, return to patient's last "normal-range" ANC monitoring interval
	BEN POPULATION Mild neutropenia is normal range for BEN population, continue treatment Obtain at least two baseline ANC concentrations before initiating treatment If treatment interrupted: < 30 days, continue monitoring as before ≥ 30 days, monitor as if new patient Discontinuation for reasons other than neutropenia	BEN POPULATION Weekly from initiation to 6 mo Every 2 wk from 6 to 12 mo Monthly after 12 mo
Severe neutropenia (< 500 cells/mm^3)[a]	GENERAL POPULATION Recommend hematology consult Interrupt treatment for suspected clozapine-induced neutropenia Do not rechallenge unless prescriber determines that benefits outweigh risks	GENERAL POPULATION Daily until ANC ≥ 1000 cells/mm^3 Three times weekly until ANC ≥ 1500 cells/mm^3 If patient rechallenged, resume treatment as a new patient under "normal-range" monitoring once ANC ≥ 1500 cells/mm^3
	BEN POPULATION Recommend hematology consult Interrupt treatment for suspected clozapine-induced neutropenia Do not rechallenge unless prescriber determines that benefits outweigh risks	BEN POPULATION Daily until ANC ≥ 500 cells/mm^3 Three times weekly until ANC ≥ a patient's established baseline If patient rechallenged, resume treatment as a new patient under "normal-range" monitoring once ANC ≥ 1000/mm^3 or at patient's baseline

[a]Confirm all initial reports of ANC > 1500 cells/mm^3 with a repeat ANC measurement within 24 hr.

[b]If clinically appropriate.

ANC = absolute neutrophil count; BEN = benign ethnic neutropenia.

Information from: Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers. (package inserts)

(a) OH, bradycardia, syncope, and cardiac arrest: Are dose related and patients are at highest risk at initiation of therapy or with rapid dose titration. Must be initiated at 12.5 mg once or twice daily, titrated slowly, and given in divided doses
(b) Seizures: Risk is dose related and can be minimized by starting low and titrating slowly.
(c) Myocarditis and cardiomyopathy: These are rare. They can occur at any point in treatment; however, myocarditis is more common in the first 2 months of treatment, and cardiomyopathy is more common after 8 weeks of treatment. Cardiomyopathy is usually delayed in onset. Risk factors for myocarditis include rapid dose titration and initiation of clozapine at high doses. If patients develop either of these, they should not be rechallenged with clozapine unless benefits are judged to outweigh risks.

ii. Additional adverse effects include weight gain, sedation, hypersalivation, rapid heart rate, anticholinergic adverse effects, and fever. The presence of fever should alert the clinician to the possibility of infection and agranulocytosis. If the drug is discontinued for 48 hours or more, retitration is required to avoid seizures or cardiac adverse effects.
iii. In January 2020, the FDA strengthened an existing warning regarding clozapine-associated constipation. It can progress to serious complications, including necrotizing colitis and intestinal ischemia, hospitalization, and death. Risk increases with clozapine dose and when clozapine is combined with other medications that can slow gastrointestinal (GI) motility. Prophylactic laxatives should be used in high-risk patients.

b. Aripiprazole
i. Aripiprazole is a partial agonist at D_2 with high affinity for the D_3 receptor. As a result, it is not associated with hyperprolactinemia.
ii. Has a low risk of most forms of EPS, including tardive dyskinesia. Is associated with a high incidence of akathisia
iii. Aripiprazole has been associated with pathological gambling and other compulsive behaviors, which may be related to its affinity for D_3 and partial agonism at D_2.
iv. Available in three LAIs: Abilify Maintena, Aristada (aripiprazole lauroxil), and Abilify Asimtufii. As with any other LAIs, patients should demonstrate tolerability with the oral formulation before receiving the injection. Abilify Maintena and Abilify Asimtufii require 14 days of overlap with oral aripiprazole or the concurrent antipsychotic. Aristada Initio is a special formulation of aripiprazole lauroxil that is intended to be given as a single 675-mg dose with 30 mg of oral aripiprazole to initiate long-acting aripiprazole lauroxil or reinitiate therapy after a missed dose of aripiprazole lauroxil. This formulation is not intended to be used as a repeat injection. If Aristada is initiated without the Initio formulation, a 21-day overlap with oral aripiprazole is required.
v. Aripiprazole is also available as a tablet that contains an ingestible event marker that detects when the medication has been taken and is tracked through a smartphone app and web portal (Abilify MyCite).

c. Asenapine
i. Available only as a sublingual formulation and as a patch.
ii. It is important to avoid eating or drinking for 10 minutes after administration of the sublingual tablet.
iii. The patch is changed daily. It can be worn while showering but has not been evaluated for bathing or swimming.
iv. Has been associated with a high risk of orthostasis and sedation
v. There has also been a warning about the risk of hypersensitivity reactions with asenapine.
vi. Use is contraindicated in severe hepatic impairment (Child-Pugh class C).

d. Brexpiprazole
i. Chemically related to aripiprazole
ii. The most common dose-dependent adverse effects are akathisia, weight gain, and somnolence. Clinically significant weight gain (greater than 7%) occurs in 8%–12% of patients. Brexpiprazole can also cause hyperglycemia and dyslipidemia.
iii. Must be adjusted for renal function (CrCl less than 60 mL/minute/1.73 m^2) and moderate to severe hepatic impairment (Child-Pugh class B or C)
iv. Like aripiprazole, brexpiprazole may increase the risk of pathological gambling and other compulsive behaviors.

e. Cariprazine
   i. Cariprazine has a half-life of 2–4 days. It also has active metabolites that have long half-lives (DCAR 1–2 days, DDCAR 1–3 weeks). Hence, changes in dose may not be reflected clinically for long periods.
   ii. Cariprazine is not recommended for patients with a CrCl of less than 30 mL/minute/1.73 m^2 or severe hepatic impairment (Child-Pugh class C).
   iii. Cariprazine is associated with dose-related OH, particularly at initiation and with dose increases.
   iv. Limited studies suggest a low rate of weight gain over 6 weeks (1%–8% incidence, with 8% of those gaining more than 7%). Other adverse drug reactions include gastrointestinal (GI) symptoms, somnolence, dizziness, parkinsonism (13%–21%), and seizures.
   v. Leukopenia and neutropenia have occurred, but there are no current recommendations for monitoring.
f. Iloperidone
   i. Iloperidone has a high risk of orthostasis but a lower risk of EPS, anticholinergic symptoms, and sedation. Iloperidone has a strict titration schedule to minimize OH. Retitration should occur if more than 3 days of medication have been missed.
   ii. Short- and long-term studies have also shown an association with QTc prolongation similar to that of haloperidol and ziprasidone.
   iii. Dosage should be adjusted for moderate intensity, and use should be avoided in severe hepatic impairment.
g. Lumateperone
   i. Has presynaptic partial agonism and postsynaptic antagonism for D_2 receptors and at least 60 times more affinity for the serotonin-2A receptor than the D_2 receptor. This is theorized to be associated with the low incidence of EPS in clinical trials. It also indirectly modulates glutamatergic activity.
   ii. The recommended starting and target doses are both 42 mg daily. It should be administered with food.
   iii. The most common adverse effects are sedation/somnolence, dry mouth, fatigue, nausea, constipation, and dizziness.
   iv. Avoid use with CYP3A4 inducers or inhibitors. It is also a substrate for glucuronosyltransferase.
   v. Avoid use in moderate and severe hepatic impairment (Child-Pugh class B or C).
h. Lurasidone
   i. Has a low risk of metabolic and cardiac effects
   ii. Dose-related EPS may occur.
   iii. Lurasidone should be taken with at least 350 kcal of food.
   iv. The dose must be tapered for moderate and severe renal impairment, when used with a moderate CYP3A4 inhibitor (e.g., diltiazem), and for moderate and severe hepatic impairment.
i. Olanzapine
   i. This drug is structurally similar to clozapine and has a similar pharmacologic profile.
   ii. Unlike clozapine, it does not require strict monitoring for agranulocytosis.
   iii. In one study, negative symptoms responded better to olanzapine than to haloperidol.
   iv. Together with clozapine, olanzapine carries the highest risk of diabetes. For this reason, many schizophrenia treatment guidelines do not consider it first-line therapy.
   v. Olanzapine is available in a short-acting parenteral formulation for the treatment of acute agitation or aggression associated with psychiatric disorders.
   vi. Olanzapine is also available as a depot injection olanzapine pamoate (Zyprexa Relprevv). Because administration of olanzapine pamoate has been associated with extreme sedation and delirium, it is part of a REMS program (called the Zyprexa Relprevv Patient Care Program).

Prescribers must undergo training, and it can only be administered within an approved institution where the patient has postdose supervision for 3 hours.

vii. Olanzapine is available in combination with samidorphan, which helps mitigate weight gain from olanzapine. Initiation of the combination should be delayed for a minimum of 7 days after last use of short-acting opioids and 14 days after last use of long-acting opioids.

j. Paliperidone
   i. The major active metabolite of risperidone. Paliperidone's pharmacologic profile is similar to that of the parent drug (see the text that follows).
   ii. Paliperidone palmitate is also available as an LAI in monthly (Invega Sustenna), 3-month (Invega Trinza), and 6-month (Invega Hafyera) formulations. As with other LAI formulations, oral tolerability should be established before changing to the LAI. No overlap with oral medication is needed for either the Trinza or Hafyera LAI formulation; however, both require one-time pretreatment with Sustenna before switching formulations.
   iii. Adjustment for renal function is required.

k. Pimavanserin
   i. Currently indicated only for psychosis associated with Parkinson disease, but is being studied as an adjunctive treatment for patients with schizophrenia who have predominantly negative symptoms
   ii. Lacks affinity for D_2 receptors. Is an inverse agonist at serotonin-2C receptors. Although classified as an SGA, it is structurally different from any other member of this class.
   iii. Has a large volume of distribution and a long half-life (55–60 hours), with an active metabolite with a half-life of 200 hours
   iv. The most common adverse effects include headache, dizziness, nausea, peripheral edema, and confusion.
   v. The dose is 34 mg once daily. It is metabolized by CYP3A4. The dose must be tapered when given with a strong 3A4 inhibitor. Pimavanserin should be avoided with strong CYP3A4 inducers.

l. Quetiapine
   i. In addition to antagonism at the D_2 and serotonin-2C receptors, quetiapine has a high affinity for histamine-1 receptors. Therefore, quetiapine has a high incidence of somnolence and weight gain. May also cause OH
   ii. Unlike other antipsychotics, quetiapine has a low incidence of EPS. Hence, quetiapine is often used for psychosis associated with Parkinson disease, despite the lack of strong evidence for efficacy.

m. Risperidone
   i. This drug is a potent dopamine D_2 antagonist and a serotonin-2C antagonist with limited anticholinergic activity.
   ii. At doses of up to 6 mg/day, the incidence of EPS has been no higher than with placebo in clinical studies. However, EPS is a dose-related phenomenon that may occur in patients taking the drug even at usual doses.
   iii. Patients often tolerate risperidone better than haloperidol. However, this increase in tolerability compared with haloperidol is lost at high doses of risperidone (i.e., adults, 6 mg/day or more or seniors, 4 mg/day or more).
   iv. Adverse effects include sedation, OH, weight gain, sexual dysfunction, and hyperprolactinemia.
   v. Dose must be tapered for CrCl less than 30 mL/minute/1.73 m^2 and severe hepatic impairment (Child-Pugh class C).
   vi. An LAI formulation that is administered intramuscularly (Risperdal Consta) is available and requires refrigeration. This formulation is administered every 2 weeks and requires a 3-week bridge therapy with oral risperidone.

vii. Risperidone is also now available as an LAI that is administered subcutaneously (Perseris and Uzedy). Neither injection requires oral overlap.
viii. Like with other LAIs, tolerability with oral therapy should be established before initiating either of the long-acting formulations of risperidone.

n. Ziprasidone
i. Has a low incidence of metabolic syndrome, but can prolong the QTc interval. Use caution if combining it with other drugs (e.g., tricyclic antidepressants [TCAs] or antiarrhythmics) that can also increase the QTc interval.
ii. Ziprasidone is also available in a parenteral formulation for acute agitation.
iii. Ziprasidone must be taken with food (at least 500 kcal) to increase absorption.
iv. Ziprasidone carries a warning for drug reaction with eosinophilia and systemic symptoms (DRESS), which can be fatal. DRESS consists of three or more cutaneous reactions (including rash or exfoliative dermatitis), eosinophilia, fever, and lymphadenopathy and one or more of the following systemic complications: hepatitis, nephritis, pneumonitis, myocarditis, and pericarditis.

J. Treatment Goals for Schizophrenia
1. Acute
a. Reduce acute symptoms.
b. Return patient to baseline level of function.
2. Maintenance
a. Prevent recurrence of symptoms.
b. Maximize functioning and quality of life.

K. Nonpharmacologic Treatment of Schizophrenia
1. A comprehensive, person-centered treatment plan should be developed and documented. Elements should include treatment setting, plans for addressing risks of harm to self or others, barriers to adherence, and goals of treatment.
2. Psychosocial interventions that benefit patients include cognitive behavioral therapy (CBT) for psychosis, psychoeducation, supported employment services, cognitive remediation, social skills training, and supportive psychotherapy.
3. Patients with schizophrenia with a history of poor engagement with services that lead to frequent relapse or social disruption, such as homelessness and legal difficulties including imprisonment, should be offered assertive community treatment.
4. Patients with schizophrenia should receive interventions aimed at developing self-management skills and enhancing person-oriented recovery.
5. When assessing adherence, a patient-centered approach is crucial, particularly if anosognosia exists. Methods that enhance the therapeutic alliance, such as motivational interviewing, and that are objective and nonjudgmental have the greatest chance of success.

L. Treatment with Antipsychotics
1. Choosing an antipsychotic: In practice, SGAs are preferred as first-line treatment. However, most guidelines recommend either an FGA or an SGA. The 2020 APA guidelines recommend individualizing treatment to the specific patient. This includes gathering information on previous treatment experiences and responses and the patient's treatment preferences and discussing the potential risk-benefit of potential medications, as well as other treatment options.

2. Therapy initiation
    a. First episode: Younger patients (children, adolescents, and young adults) or treatment-naive patients may be more sensitive to adverse effects and may respond more quickly to treatment. Hence, it is recommended to start with a lower dose. This may also improve chances of adherence by avoiding adverse effects. Early LAI use has shown benefit in first episodes.
    b. In patients with a history of treatment with antipsychotics, higher doses and more aggressive titrations may be appropriate.
    c. Older individuals with concomitant physical health issues and medications may need starting doses that are as small as one-fourth to one-half the usual adult starting dose.
    d. Once medication is initiated, escalation to a therapeutic dose can be achieved relatively rapidly, though this will vary depending on the individual drug.
3. Dose optimization:
    a. Can be difficult to determine during the acute phase because it may take patients 2–4 weeks to show an initial response with conservative titration; often, more aggressive titration is used for inpatients to hasten response. This must be weighed against the increased risk of adverse effects. It may take longer to show optimal response.
    b. Data suggest that patients who have experienced less than a 20% response after 2 weeks on a therapeutic dose are unlikely to be much improved at 4–6 weeks (as reflected by a 50% or greater reduction in symptoms). Thus, response should be assessed at 2–4 weeks after achieving a therapeutic dose.
    c. Patients should continue to be treated with the same medication that improved their symptoms while carefully monitoring for adverse effects, particularly development of metabolic syndrome. Development of metabolic syndrome or problematic adverse effects requires a change in medication to decrease patient-driven cessation of therapy.
4. Therapy duration: The chronicity of schizophrenia usually results in lifelong antipsychotic treatment. Benefits of a particular medication must be weighed against long-term adverse effects (e.g., tardive dyskinesia) when selecting a specific antipsychotic. Relapse rates within the first year of medication discontinuation are greater than 50%; thus, maintaining the antipsychotic at the minimal effective dose continuously may be the best approach for most patients. Long-term therapy should include monitoring for metabolic complications such as diabetes, weight gain, and lipid abnormalities, as well as abnormal movements.
5. Any changes in antipsychotics (other than between FGAs) or discontinuations should be performed gradually to avoid withdrawal symptoms.
6. Treatment-resistant schizophrenia: Clozapine is the agent of choice. See the Clozapine section earlier for more details.
7. Use of several antipsychotics: Current data do not support routine combination of antipsychotics. Some data suggest benefit for augmenting clozapine, but more information is needed.

M. Adjunctive Medications
1. Lamotrigine may be beneficial when added to clozapine in patients with partial response. Data do not support the use of other antiseizure medications, including valproate, carbamazepine, and topiramate.
2. Benzodiazepines: May be useful during the acute phase for agitation or anxiety but are less effective for psychotic symptoms. These drugs must also be used with caution in patients with schizophrenia because this population is at high risk of substance use disorder (SUD).
3. Antidepressants are indicated when patients with schizophrenia develop depression.
4. Dexmetomidine, an alpha2-adrenergic agonist with anesthetic and sedative properties, can be used to treat agitation associated with schizophrenia in the acute setting.

Patient Case

Questions 5–8 pertain to the following case.

A 45-year-old has a medical history significant for sleep apnea, hypertension, type 2 diabetes, chronic pain, and bulimia. The current clinic visit is for an assessment of depressive symptoms and a medication evaluation. Endorsed symptoms include sad mood, poor appetite (lost 6.8 kg [15 lb]), poor concentration, and feelings of hopelessness and worthlessness for the past 3 weeks. The patient has also stopped going to book club because of lack of motivation to get out of the house, and there are frequent nocturnal awakenings. The patient denies suicidal or homicidal ideation. The patient also denies any use of alcohol, tobacco, or illicit drugs. Current medications include hydrochlorothiazide, metformin, hydrocodone/acetaminophen, and aspirin. Current BMI is 20 kg/m^2, and blood pressure today is 152/94 mm Hg. The patient reports adherence to current medications.

5. Which selective serotonin reuptake inhibitor (SSRI) would most likely interact with the current medications?
   A. Citalopram.
   B. Fluvoxamine.
   C. Paroxetine.
   D. Sertraline.

6. Which antidepressant would be most appropriate for the depressive symptoms?
   A. Bupropion.
   B. Fluoxetine.
   C. Mirtazapine.
   D. Venlafaxine.

7. It has been 4 weeks since the initial visit with you, and the patient has been treated with citalopram 20 mg/day in the morning. Sad mood persists, but insomnia, concentration, and appetite have improved. Persistent symptoms include feelings of hopelessness and worthlessness, lack of motivation, and anhedonia. No adverse effects exist. At this point, which is the best recommendation to optimize therapy?
   A. Continue citalopram 20 mg/day.
   B. Increase citalopram to 40 mg/day.
   C. Add aripiprazole.
   D. Change to a different SSRI.

8. Six months later, depression symptoms have resolved, but citalopram is causing anorgasmia, which is unacceptable to the patient. Which is the most appropriate recommendation at this time?
   A. Discontinue citalopram.
   B. Add bupropion to citalopram.
   C. Change to a different SSRI.
   D. Change to vortioxetine.

II. MAJOR DEPRESSIVE DISORDER (MDD)

A. Identification of Depressive Disorders. This overview is based on the *DSM-5-TR*; please consult for complete diagnostic criteria.
   1. MDD is also called unipolar depression, or just depression. MDD is diagnosed when a patient has at least five of the following symptoms almost every day for at least 2 weeks:
      a. Must have a depressed mood or anhedonia (loss of interest in pleasurable activities)
      b. Additional symptoms include sleep disturbances, changes in weight or appetite, decreased energy, feelings of guilt or worthlessness, psychomotor retardation or agitation, decreased concentration, and suicidal ideation.
      c. The symptoms must interfere with the patient's everyday ability to function.
   2. Persistent depressive disorder (dysthymia): Chronic depressed mood occurring more days than not for at least 2 years but that does not meet the criteria for MDD.

B. Assessment of Patients with MDD
   1. Psychiatric history: A thorough history of symptoms is compared with the diagnostic criteria, and the diagnosis is made from the collected data.
   2. Clinician rating scales: Psychometric instruments used to identify depression and assess its severity. Common examples include:
      a. Hamilton Rating Scale for Depression (HAM-D/HDRS): Often used to show efficacy in clinical trials for FDA approval of antidepressants. A common clinical trial enrollment score is greater than 18 (moderate-severe depression). A response is usually defined as at least a 50% reduction in the HAM-D score. "Remission" is a return to a normal state or a HAM-D of 7 or less.
      b. CGI (Clinical Global Impressions) scale is a clinician-rated scale that evaluates the severity and improvement of patients overall.
      c. MADRS (Montgomery-Åsberg Depression Rating Scale) also evaluates symptoms of depression. It is commonly used in clinical trials.
   3. Patient rating scales: Patient-completed rating instruments. Answers to the questions are used to identify and assess the level of depression.
      a. Patient Health Questionnaire-9 (PHQ-9) is based on the *DSM-5-TR* diagnostic criteria for major depression. The PHQ-9 is easily administered and assessed. For this reason, it is often used in the primary care setting. Patients can be screened with an abbreviated version (the PHQ-2). If patients test positive, the PHQ-9 is administered. The PHQ-9 can also be used to monitor treatment response.
      b. Beck Depression Inventory (BDI)
      c. Quick Inventory of Depressive Symptoms (QIDS): Self-Rated
      d. Geriatric Depression Scale (GDS)
   4. Physical examination and laboratory tests: Necessary to rule out physical causes (e.g., thyroid disorders, vitamin deficiencies) that may mimic symptoms of depression
   5. Biologic testing: Depression is commonly associated with abnormalities in the dexamethasone suppression test and tests of the thyroid axis. However, these tests are not routinely used in clinical practice.
   6. Medications and substances (e.g., interferons, benzodiazepines, barbiturates, alcohol, central nervous system [CNS] depressants, withdrawal from stimulants [cocaine, amphetamines]) can have depression as an adverse effect. Pharmacists should perform a medication and substance use review to identify possible causes.
   7. All patients should be screened for suicidal ideation.
      a. The National Suicide Hotline is 988.
      b. The website is https://988lifeline.org/.

C. Therapeutic Options
   1. Nonpharmacologic treatment options: Examples include interpersonal psychotherapy and CBT. It takes longer to achieve effective results with psychotherapy than with pharmacotherapy. Psychotherapy may have broader and longer-lasting effects than pharmacotherapy monotherapy. Psychotherapy is recommended as monotherapy for initial treatment in patients with mild to moderate MDD (CBT and interpersonal therapy have the best evidence). Psychotherapy combined with pharmacotherapy is recommended for moderate to severe depression. Combination is more effective than either intervention alone.
   2. Pharmacotherapy: Antidepressant therapy may lead to a more rapid response than psychotherapy, but when discontinued, there is a risk of relapse and adverse effects.
   3. Electroconvulsive therapy (ECT): Option for refractory depression, depression in pregnancy, psychotic depression, and other conditions for which medications may not be optimal or effective. The usual induction cycle is two or three treatments per week for 6–12 treatments. Maintenance dosing is individualized to the patient, and frequency can vary from weekly to monthly. Temporary memory loss is common, and medications that affect seizure threshold must be tapered or held before treatment. ECT is also suggested as initial treatment if symptoms are severe or life threatening.

D. Pharmacotherapeutic Options: Considerations and Keys to Use
   1. Selection: All antidepressants are considered equally efficacious. First-line medications include selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), bupropion, mirtazapine, and vortioxetine. Consider possible drug-drug and drug-disease interactions, concurrent illnesses, prior responses, family members' prior responses, patient preference, and cost.
   2. Adequate trial: An adequate trial includes the correct drug for the patient at a therapeutic dose for an appropriate duration. A therapeutic trial lasts 4–8 weeks.
   3. Response and remission: A response is usually defined as a 50% reduction in symptoms. Remission is a return to normal mood (e.g., HAM-D of 7 or less; PHQ-9 less than 5). Remission is also defined as at least 3 weeks with no symptoms of depressed mood and anhedonia and no more than three remaining symptoms of depression. Remission is the goal of therapy. Optimizing the dose or duration is important for achieving remission.
   4. Treatment phases
      a. Acute
         i. The goal of this phase is remission.
         ii. Onset of antidepressant effect: Physical symptoms (energy levels, sleep disturbances) improve before affective symptoms. For this reason, patients with suicidal ideation may be at an increased risk of carrying out plans during this phase and should be closely monitored. Early response (20%–30% reduction in symptoms) in the first 2–4 weeks is a strong predictor of remission at 12 weeks. A patient who has a partial response in the first 4 weeks should be allowed a longer trial (and at the full therapeutic dose) before moving on to other therapy. In general, it takes 4–6 weeks to see the full effect of antidepressants, given the correct drug, dose, and adherence, but it may take as long as 8 weeks to see a response. Remission may take up to 12 weeks.
         iii. Monitoring therapy: Patients should be monitored for response through interviews or by repeating rating scales. In addition, patients (and their support systems, if available) should be educated about therapy and closely monitored for adverse effects. Although most of the adverse effects are not life threatening, they may affect adherence.
         iv. Nonresponders: A nonresponder can be changed to another antidepressant within either the same class or a different class. A patient who does not respond to one SSRI may respond to another in the same class, as shown in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial.

b. Maintenance
   i. Once a patient has achieved remission, treatment should continue for at least another 6–9 months.
   ii. Those with risk factors for recurrent depression should receive treatment for 2 years or longer. Risk factors include frequent, recurrent episodes; severe episodes (including psychosis, severe impairment, or suicidality); chronic episodes; presence of comorbid psychiatric or medical conditions; and presence of residual symptoms or difficult-to-treat episodes.

5. Efficacy of antidepressants according to rigorous clinical trials occurs in 60%–70% of patients, regardless of drug. Effectiveness, which is more reflective of clinical practice, is lower, about 50%–60%. The remission rate with one antidepressant trial is about 30%, as seen in the STAR*D trial.
6. Drug interactions (Table 6): Many antidepressants are metabolized or inhibited by CYP enzymes.

Table 6. Antidepressants and the CYP System[a]

	1A2	2C19	2D6	3A4
Substrate	Duloxetine	Citalopram Escitalopram Fluoxetine Imipramine Vilazodone	Amitriptyline Desipramine Duloxetine Fluoxetine Imipramine Nefazodone Nortriptyline Trazodone Venlafaxine Vortioxetine	Citalopram Escitalopram Levomilnacipran Nefazodone Trazodone Venlafaxine Vilazodone
Inducer	Cannabis (smoking) Tobacco (smoking)	St. John's wort		St. John's wort
Inhibitor	Caffeine (high dose) **Fluvoxamine**	Amitriptyline Cannabis Fluoxetine Fluvoxamine Imipramine	**Bupropion**[b] Cannabis Duloxetine **Fluoxetine** **Paroxetine** Sertraline	Fluvoxamine **Nefazodone**

[a]Boldface type in table body indicates strong inhibitor.

[b]Metabolized by CYP2B6.

E. Selective Serotonin Reuptake Inhibitors (Table 7)
   1. SSRIs selectively inhibit the reuptake of serotonin into the presynaptic neuron and desensitize the presynaptic serotonin autoreceptor, resulting in increased serotonin concentrations. Two additional SSRIs, vortioxetine and vilazodone, have additional activity and are covered separately in the text that follows.

Table 7. SSRI Characteristics

Characteristic	Citalopram (Celexa)	Escitalopram (Lexapro)	Fluoxetine (Prozac)	Fluvoxamine[a] (Luvox)	Paroxetine (Paxil)	Sertraline (Zoloft)
Half-life	32 hr	27–32 hr	1–4 days	15 hr	21 hr	26 hr
Active metabolite	No	No	Yes[b]	No	No	No
Usual dose (mg/day)	20–40	10–20	20–60	50–300	10–60	50–200
Maximum daily dose (mg)	40 20 (age > 60)	20	80	300	50 (depression) 60 (anxiety)	200

[a]Indicated only for obsessive-compulsive disorder; seldom used for depression.

[b]Norfluoxetine.

2. The efficacy of SSRIs is equal for the treatment of depression. Adverse effect profiles differ slightly, and patients may tolerate one SSRI better than another.
3. Blockade of serotonin reuptake leads to an increase in serotonin overall and may influence all subtypes of serotonin receptors. Some (serotonin-2A, -2C, -3, and -4) may be responsible for some of the unwanted adverse effects (e.g., insomnia, restlessness, GI concerns). Activation, agitation, anxiety, or panic may occur in some patients, especially during the early phase of therapy. The most common adverse effects associated with this class of agents include GI concerns, insomnia, restlessness, headache, and sexual dysfunction. In general, the most activating SSRIs are fluoxetine and sertraline, whereas paroxetine and fluvoxamine are the most sedating. Citalopram and escitalopram have no appreciable sedating or activating effects. Sexual dysfunction is more common than reported in the prescribing information and may occur in 50% or more of patients receiving these agents. Interventions to consider for SSRI-induced sexual dysfunction include using the wait-and-see method, adding bupropion, and lowering the SSRI dose. PDE-5 (phosphodiesterase type 5) inhibitors may be beneficial for men with erectile dysfunction. Data are less robust for women. Other interventions with weaker data include adding buspirone and mirtazapine.
4. Because these drugs have such potent serotonergic activity, combinations with other drugs affecting serotonin can lead to serotonin syndrome. Examples include the monoamine oxidase inhibitors (MAOIs), dextromethorphan, meperidine, tramadol, sympathomimetics, linezolid, lithium, TCAs, and SNRIs. Although triptans have traditionally been listed among the agents to watch, a 2010 statement released by the American Headache Society reports poor evidence for the interaction. The finding was supported by a 2018 article (JAMA Neurol 2018;75:566-72) suggesting that the FDA reconsider the advisory. Triptans bind to different serotonin receptors than SSRIs or SNRIs and thus pose a low risk. Serotonin syndrome includes symptoms from three clusters: neuromuscular hyperactivity (e.g., myoclonus, rigidity, tremors, incoordination), altered mental status (agitation, confusion, hypomania), and autonomic instability (hyperthermia, diaphoresis). Serotonin syndrome can be subtle in onset or confused with NMS. Several criteria exist to identify serotonin syndrome, with the Hunter criteria considered the most accurate. These rely heavily on neurologic findings, with the presence of clonus being the most prominent, though tremor plus hyperreflexia are also considered adequate for diagnosis. Treatment includes discontinuing the offending agent, providing supportive measures such as cooling blankets and respiratory assistance, and providing cyproheptadine; a benzodiazepine for myoclonus; antiseizure medications; and nifedipine for hypertension.
5. SSRIs have been associated with EPS, including akathisia, dystonia, and bradykinesia, but these are uncommon. EPS appears to result from an effect of serotonin on dopaminergic neurotransmission in the basal ganglia.
6. SSRIs can cause hyponatremia of the SIADH (syndrome of inappropriate antidiuretic hormone secretion) type, particularly in older adult patients. Individuals should be monitored for symptoms suggestive of hyponatremia.
7. A withdrawal syndrome has been observed, especially for the drugs with shorter half-lives, so a gradual dose reduction (e.g., over 2–4 weeks) may be indicated. Symptoms include flu-like symptoms, such as nausea and chills, and neurologic symptoms, such as paresthesias, insomnia, anxiety, and "electric shock"–type sensations. If the problem is severe or persists, the SSRI can be reinitiated and the dose gradually reduced again. The timing of withdrawal syndrome symptoms correlates with SSRI half-life, so withdrawal symptoms occur the earliest with paroxetine. Even though fluoxetine has a significantly longer half-life, withdrawal symptoms may still occur and be delayed in onset.
8. The FDA ordered changes to citalopram package labeling, limiting the daily dose to no more than 40 mg because of an increased risk of QTc prolongation at daily doses greater than 40 mg. Patients who have risk factors for QTc prolongation (congenital long QTc syndrome, bradycardia, hypokalemia, hypomagnesemia, recent acute myocardial infarction, and uncompensated heart failure) or who are taking concomitant medications that may increase the QTc interval should not be treated with citalopram.

The maximum recommended citalopram dose is 20 mg/day for patients with hepatic impairment, patients who are older than 60, patients who are 2C19 poor metabolizers, or patients who are taking concomitant 2C19 inhibitors. Studies in these populations taking 40 mg daily have failed to find an increase in mortality despite the warning.

9. These drugs are not as lethal in overdose cases as TCAs.
10. All SSRIs listed in Table 7 are available in generic form. The low cost, better tolerability, and safety of SSRIs warrant their use as first-line treatment of MDD in most patients.
11. Extended-dosing formulations: Fluoxetine 90 mg can be taken once weekly. Fluoxetine 90 mg is taken only during continuation therapy rather than as initial treatment. It is not commonly used in clinical practice. Paroxetine controlled release (CR) may have lower rates of nausea in the first week of treatment; efficacy is comparable, and both formulations are administered once daily. The weekly and CR products are available in generic form but are higher in cost.
12. Escitalopram is the *S*-isomer of citalopram and is the active component of the racemic mixture. At a 10-mg dose, escitalopram is at least as effective as citalopram 20 mg, but at this dose, there are fewer adverse effects. At higher doses, this advantage is not as pronounced.
13. SSRIs appear to modestly increase the risk of bleeding by inhibiting the serotonin reuptake into platelets. This leads to a decrease in serotonin-mediated platelet activation. Case-control and cohort studies also suggest an increased incidence of both vertebral and non-vertebral bone fractures.

F. Serotonin-Norepinephrine Reuptake Inhibitors (Table 8)

Table 8. SNRI Characteristics

Characteristic	Desvenlafaxine (Pristiq)	Duloxetine (Cymbalta)	Levomilnacipran (Fetzima)	Venlafaxine (Effexor)
Half-life	10–11 hr	8–17 hr	21–29 hr	5–11 hr
Active metabolite	No	No	No	Yes
Usual dose (mg/day)	50	60	40–120	75–225
Maximum daily dose (mg)	100[a]	120[b]	120	225

[a]Doses > 50 mg do not necessarily confer further benefit.

[b]Doses of ~60 mg do not necessarily confer further benefit for depression. Higher doses are beneficial for anxiety and pain.

1. Venlafaxine, desvenlafaxine, duloxetine, and levomilnacipran block the reuptake of norepinephrine and serotonin. Although milnacipran is considered an SNRI, it is only FDA approved for fibromyalgia. Unlike TCAs, SNRIs have negligible effects at other receptors that cause anticholinergic or antihistaminic adverse effects, with the possible exception of duloxetine, which appears to have a slightly higher incidence of anticholinergic symptoms. Venlafaxine has a dose-related effect on norepinephrine compared with desvenlafaxine and duloxetine. At doses of less than 150 mg/day, venlafaxine is a serotonin reuptake inhibitor.
    a. Whether the dual action of venlafaxine makes it more effective than SSRIs is an area of continued research. Some patients (e.g., treatment nonresponders or those with significant anhedonia) appear to benefit either from agents that affect norepinephrine and serotonin or from combinations of drugs with that effect.
    b. The adverse effect profile of venlafaxine is similar to that of the SSRIs, with GI concerns being common. Of note, SNRIs can cause increases in blood pressure, which are usually mild and not clinically significant unless the patient has uncontrolled hypertension. This is a dose-related phenomenon, as described earlier, particularly for venlafaxine and desvenlafaxine. Levomilnacipran and desvenlafaxine are also associated with OH.

2. Levomilnacipran is the more potent enantiomer of milnacipran. Levomilnacipran is only approved for depression, not fibromyalgia. The dose must be adjusted in renal insufficiency, and the drug is not recommended in end-stage renal disease. Levomilnacipran can cause hyponatremia and increase bleeding risk. The capsule should not be crushed or opened. Levomilnacipran is metabolized through CYP3A4 (major pathway) and CYP2C19 and CYP2D6, among others (minor pathways). Monitor signs and symptoms of potential toxicities if CYP3A4 inhibitors are used concomitantly. Both blood pressure elevations and OH can occur. Levomilnacipran can cause an elevated heart rate and palpitations, which are common reasons for discontinuation. Levomilnacipran is a more potent inhibitor of norepinephrine than venlafaxine or duloxetine (norepinephrine is slightly preferred to serotonin).
3. All SNRIs can produce serotonin syndrome. In overdose situations, both duloxetine and venlafaxine have been associated with higher rates of death than SSRIs. The risk of death because of overdose of SNRIs is still lower than with TCAs.
4. Duloxetine has also been approved for the treatment of diabetic peripheral neuropathy, fibromyalgia, and chronic musculoskeletal pain caused by chronic lower back pain or osteoarthritis pain. Be careful when using this drug with 2D6 inhibitors. Monitor blood pressure because increases have been observed. Duloxetine can cause liver toxicity and should not be used in patients with hepatic insufficiency, end-stage renal disease requiring dialysis, or severe renal impairment.
5. SNRIs can cause a withdrawal syndrome similar to the SSRIs and thus should be tapered slowly when discontinued.
6. Desvenlafaxine is an active metabolite of venlafaxine. Benefits over the parent drug are limited. Because it bypasses CYP metabolism, it may be advantageous in patients with hepatic insufficiency or those taking major 2D6 inducers or inhibitors.
7. Renal dosing is required for both desvenlafaxine and levomilnacipran.

G. Mixed Serotonergic Medications
1. Vilazodone (Viibryd) is an SSRI with partial agonist activity at the serotonin-1A receptor, which may be altered in depression and anxiety. Vilazodone has a half-life of 25 hours but does not have active metabolites. Both the usual and maximum doses are 40 mg daily. Vilazodone should be taken with food. The most common adverse effects are nausea and diarrhea. Vilazodone may cause a lower incidence of sexual dysfunction than other SSRIs and SNRIs. Vilazodone should not be used in patients with a history of seizure disorder. The dose must be decreased when given with strong 3A4 inhibitors. Postmarketing reports include acute pancreatitis and sleep paralysis, but the true frequency is unknown, and the FDA labeling has not been changed.
2. Vortioxetine (Trintellix) is an SSRI, but its pharmacologic profile differs from other SSRIs. Vortioxetine has additional agonist activity at the serotonin-1A receptor, partial agonist activity at the serotonin-1B receptor, and antagonistic activity at the serotonin-3, serotonin-1D, and serotonin-7 receptors. The clinical significance of vortioxetine's effect on the serotonin receptors is currently unknown, but in patients with depression, it also appears to improve measures of cognitive function that appear independent of its antidepressant effects. Vortioxetine has a half-life of 66 hours and no active metabolites. The starting and usual dose is 10 mg daily, with a maximum daily dose of 20 mg. Vortioxetine is metabolized by 2D6, and the maximum dose for poor metabolizers or patients taking a strong CYP2D6 inhibitor is 10 mg daily. Vortioxetine also appears to be associated with a lower incidence of sexual dysfunction than other SSRIs and SNRIs. Common adverse effects include nausea, dizziness, vomiting, xerostomia, and diarrhea or constipation.
3. Trazodone (Desyrel): A serotonin reuptake inhibitor that also blocks serotonin-2A receptors. Trazodone does not cause anticholinergic or cardiotoxic effects, as do the TCAs, but it still causes OH and sedation. Because of its sedative properties (mediated by histamine-1 antagonism), trazodone is often used for insomnia but at lower doses than for depression. It is important to be aware of the potential for

priapism, even though it is rare (0.1% or less). Patients should be educated about this risk, and it should be treated as a medical emergency.

4. Nefazodone (Serzone): Nefazodone is a serotonin-2A antagonist like trazodone, but it also blocks the reuptake of serotonin and norepinephrine. Some have called this class "serotonin antagonist reuptake inhibitors" (serotonin-2A antagonist/reuptake inhibitors). Unlike trazodone, nefazodone has minimal effects on sexual function and is less likely to cause OH. Data suggest that the serotonin-2A–blocking activity makes nefazodone more effective for anxiety associated with depression. Nefazodone's short half-life makes it necessary to administer doses twice daily. The most common adverse effects include sedation, GI concerns, dry mouth, constipation, confusion, and light-headedness. Because nefazodone is a potent inhibitor of CYP3A4, caution is necessary when using it concomitantly with drugs metabolized by this system. Given the potential for liver toxicity and its boxed warning, nefazodone is now considered a second- or third-line agent. Liver function tests must be monitored if nefazodone is used.

H. Mirtazapine (Remeron)
   1. Mirtazapine is an antagonist of presynaptic α_2-autoreceptors and heteroreceptors, which results in an increase in norepinephrine and serotonin release in the synapse. In addition, the drug blocks serotonin-2A (resulting in minimal to no sexual dysfunction, anxiety, or sedation), serotonin-3 (no nausea or GI disturbances), and serotonin-2C (weight gain) receptors.
   2. Although mirtazapine is better tolerated than the TCAs, it still has a pronounced sedative effect, together with increased appetite, weight gain, constipation, and asthenia.
   3. Abnormal liver function tests may occur, and there appears to be a very small risk of neutropenia or agranulocytosis.
   4. Lower doses may be sedating, whereas higher doses may cause insomnia.

I. Bupropion (Aplenzin, Forfivo, Wellbutrin)
   1. Bupropion is primarily an inhibitor of dopamine and norepinephrine reuptake with minimal effects on serotonin. Bupropion's exact mechanism of action remains to be defined. The parent drug blocks dopamine reuptake, whereas the metabolite blocks norepinephrine reuptake.
   2. The most important adverse effect is increased risk of seizures. This risk can be minimized by the following:
      a. Avoid use in susceptible patients (e.g., history of seizure disorder, eating disorders).
      b. Do not give more than 150 mg/dose or 450 mg/day (immediate release [IR] or ER) or 400 mg/day (sustained release [SR]).
      c. Avoid dosage titration more often than every 4 days for SR or XL and every 3 days for IR.
      d. The SR and XL products may also cause fewer adverse effects; they have largely replaced the IR tablets.
   3. The most common adverse effects include insomnia, anxiety, irritability, headache, and decreased appetite. Bupropion may also increase energy and cause psychosis in susceptible individuals. As noted previously, bupropion may actually improve sexual function; thus, it may be useful in patients not tolerating other agents for this reason. Bupropion has also been used off-label for attention-deficit/hyperactivity disorder and may help with concentration.
   4. Bupropion is available in combination with dextromethorphan (Auvelity) for the treatment of depression.

J. Tricyclic Antidepressants
   1. TCAs are effective, but adverse effects have limited their use. Now that newer agents with more tolerable adverse effect profiles are available, TCAs are used less often. TCAs have several off-label uses such as treatment for pain syndromes, migraine prophylaxis, and anxiety disorders.

2. TCAs block serotonin and norepinephrine uptake. Tertiary amines such as amitriptyline and imipramine are more potent for serotonin uptake and are metabolized to active secondary amines. The corresponding secondary amines (nortriptyline and desipramine, respectively) are more selective for norepinephrine and have less anticholinergic activity.
3. TCAs have α-adrenergic blockade, antihistaminic effects, and anticholinergic effects, leading to orthostasis, sedation, and anticholinergic symptoms, respectively. TCAs can cause sexual dysfunction.
4. TCAs can be cardiotoxic in overdose, causing prolonged QTc intervals and torsades de pointes as well as seizures (Table 9). An ECG should be monitored in patients older than 40 years who are initiated on TCAs. An actively suicidal patient should not receive a TCA.

Table 9. Adverse Effect Profile of Commonly Used TCAs

Drug	Anticholinergic	Sedation	Orthostatic Hypotension	Cardiotoxicity
Tertiary amines				
Amitriptyline	High	High	Moderate	High
Imipramine	Moderate	Moderate	High	High
Secondary amines				
Desipramine	Low	Low	Moderate	Moderate
Nortriptyline	Moderate	Moderate	Low	Moderate

5. TCAs are not recommended in patients with cardiac disease or seizure disorders. Patients at risk of OH are at increased risk of falls if they take these agents, and appropriate caution should be taken.
6. TCA serum concentrations can confirm adherence or toxicity. However, this is an infrequent clinical practice.
7. A withdrawal syndrome occurs if these drugs are discontinued too quickly. Symptoms reflect the reversal of anticholinergic effects and include lacrimation, nausea, and diarrhea, with insomnia, restlessness, and possible balance problems. Gradual dose reductions help reduce these symptoms.

K. Monoamine Oxidase Inhibitors
1. MAOIs irreversibly block the enzyme responsible for the breakdown of certain neurotransmitters, such as norepinephrine. There are two forms of this enzyme (MAO-A and MAO-B), and drugs can block one or both of them.
2. Nonselective MAOIs (isocarboxazid, phenelzine, and tranylcypromine) are available in the United States.
3. Patients taking MAOIs must be educated and monitored to avoid foods high in tyramine (e.g., aged cheese, preserved meats, wine, beer) because of the potential for precipitating a hypertensive crisis. A dietary consultation can be helpful in this respect.
4. Drug interactions with MAOIs are considerable and include over-the-counter decongestants, antidepressants, stimulants, and antihypertensives. When changing a patient from another antidepressant to an MAOI, it is prudent to wait 2 weeks after the antidepressant is discontinued before initiating the MAOI (except for fluoxetine, in which case the waiting period should be 5–6 weeks, and vortioxetine is 3 weeks) to avoid serotonin toxicity. When a patient is changed from an MAOI to another antidepressant, a 2-week washout period is usually adequate.
5. Selegiline (MAO-B inhibitor) is available in a patch formulation for depression. Selegiline is available in doses of 6 mg/24 hours, 9 mg/24 hours, and 12 mg/24 hours. Once the dose reaches 9 mg/24 hours, an MAOI diet is required. How this drug compares with other antidepressants remains unknown.

L. Gepirone
   1. Gepirone is an antidepressant approved in September 2023.
   2. It is a member of the azapirone group with serotonin-1A agonist properties and is related to buspirone (see Anxiety section).
   3. Gepirone prolongs the QT interval, so an ECG should be performed at baseline and after dose increases in patients with risk factors for QTc prolongation.
   4. The most common adverse effects include nausea, dizziness, and headache.
   5. Absorption of gepirone is increased when administered with food.
   6. Gepirone is extensively metabolized by CYP3A4 to two active metabolites, 1-(2-pyrimidinyl)-piperazine (1-PP) and 3'-OH-gepirone.
   7. Gepirone does not appear to have negative effects on sexual function.

M. Antidepressants and Suicidality: All antidepressants have an FDA boxed warning for an increased risk of suicidal thinking and behaviors in children, adolescents, and young adults (up to 24 years of age). Risk is highest at treatment initiation or dose adjustment. Other signs to watch for include agitation and anxiety (activation syndrome) and other symptoms that are unlike the patient's presenting symptoms of depression. A medication guide must be distributed before antidepressants are dispensed. The warning should not preclude antidepressant use in children, adolescents, and young adults because suicide is the second leading cause of death in this population. The results of three meta-analyses show that antidepressants decrease suicidal thoughts and acts in patients age 25–64 and decrease suicidal acts in those older than 65. The number needed to treat for an SSRI in an adolescent with depression to prevent suicidal thoughts and acts is 4–10.

N. Partial Response to Antidepressant Treatment
   1. Ensure the patient is adherent and has received a therapeutic trial (as defined in section D2 earlier) of medication.
   2. Patients can either be changed to a new antidepressant or receive adjunctive therapy. The 2016 Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines have a helpful algorithm and tables (see References section).
   3. An antidepressant with a different mechanism of action can be added (e.g., bupropion or mirtazapine to an SSRI or SNRI). Data are not strong for this practice. Use caution when combining agents to avoid potential serotonin syndrome with at-risk agents.
   4. SGAs may be used as adjuncts to antidepressant therapy. Almost all SGAs have been used, but only aripiprazole, brexpiprazole, cariprazine, and quetiapine ER have received FDA approval for this indication. Evidence also supports the use of risperidone. Olanzapine in combination with fluoxetine is also approved, but specifically for treatment-resistant depression.
   5. Ketamine infusions are used off-label for depression and suicidality, particularly in patients who are not responsive or who are only partly responsive to antidepressants.
   6. Other adjuncts include lithium, liothyronine, stimulants (including methylphenidate and modafinil), and buspirone.

O. Treatment-Resistant Depression
   1. Has many definitions; usually defined as inadequate response to at least two antidepressants
   2. FDA-approved treatment options
      a. Olanzapine plus fluoxetine: Initial dosing is 6 mg/25 mg once daily; usual dosing is 6–18 mg/25–50 mg daily.
      b. Esketamine (intranasal; Spravato)
         i. Approved for use in conjunction with an oral antidepressant
         ii. Also approved for major depression with suicidality

iii. Mechanism of action: NMDA (*N*-methyl-D-aspartate) antagonist
iv. Onset for treating depression symptoms is within hours.
v. Dosing occurs in two phases: twice weekly during the induction phase, which lasts for 2 weeks, followed by the maintenance phase, in which dosing is weekly for 4 weeks and then every 1–2 weeks thereafter.
vi. Carries boxed warnings for sedation, dissociation, abuse and misuse (controlled substance, schedule III), and suicidal thoughts and behaviors
vii. Common adverse reactions: Increased blood pressure, dissociative reactions including derealization and depersonalization, sedation, dizziness, anxiety, nausea, vomiting, and dysgeusia. Long-term use or misuse of ketamine has also been associated with ulcerative or interstitial cystitis. This has not been observed with esketamine in clinical trials but should be monitored.
viii. Only available through a REMS program in which patients must be enrolled. Only approved pharmacies can dispense, and agent must be administered in a certified health care setting where patients are observed for at least 2 hours after administration. During this time, mental status and blood pressure must be monitored. Patients cannot drive until the following day.

Patient Cases

Questions 9–11 pertain to the following case.

A 26-year-old with a history of type I bipolar disorder presents to the inpatient unit. Their spouse found them withdrawing their life savings from the bank. The patient states that they are the perfect candidate for the presidency. The patient has not slept in the past 48 hours and is hyperverbal. The patient is placed on an involuntary mental health hold for control of manic symptoms. There is a history of nonadherence to medications and the patient currently takes none. The last hospitalization was 2 months ago, when the patient had significant depressive symptoms and suicidal ideation. The patient has three or four hospitalizations per year. Previous medication trials include olanzapine and lamotrigine. The patient has also been given a diagnosis of hepatitis C with AST 175 U/L and ALT 186 U/L.

9. Which mood stabilizer is most appropriate for this patient at this time?
   A. Carbamazepine.
   B. Divalproex sodium.
   C. Lamotrigine.
   D. Lithium.

10. Which treatment-emergent adverse effect would be of most concern and would require immediate evaluation if lithium were prescribed?
   A. Hypothyroidism.
   B. Coarse tremor.
   C. Severe acne.
   D. Weight gain.

Patient Cases *(Cont'd)*

11. Three months later, the patient's condition has been stable on lithium 900 mg/day. Today, during a clinic visit, they are confused and slurring their words. The current lithium serum concentration is 1.9 mEq/L. Current medications include amlodipine for hypertension, atorvastatin for dyslipidemia, and zolpidem for sleep. They began running a week ago. They have been replacing fluids using an oral rehydrating solution (Gatorade) and taking ibuprofen around-the-clock for pain. Which most likely contributed to this patient's current clinical situation?
    A. Amlodipine.
    B. Gatorade.
    C. Ibuprofen.
    D. Zolpidem.

12. A 36-year-old woman (BMI 20 kg/m^2) with type I bipolar disorder presents to your clinic tearful, with a 2-week history of depressed mood, anhedonia, insomnia, feelings of worthlessness, and loss of appetite. She has passive thoughts of suicide, but no concrete plan. She currently takes lithium, with a trough serum concentration of 1.1 mEq/L. Which medication would be best to treat her current episode?
    A. Divalproex sodium.
    B. Lamotrigine.
    C. Quetiapine.
    D. Venlafaxine.

III. BIPOLAR DISORDER

A. Overview of Bipolar Disorder
    1. The *DSM-5-TR* defines bipolar disorder by the experience of a manic or hypomanic episode. Mania can be thought of as the affective opposite of depression. Consult the *DSM-5-TR* for a complete description of the diagnostic criteria. A manic episode is characterized by at least 1 week (or any duration, if hospitalization needed) of an abnormal and persistently elevated, expansive, or irritable mood accompanied by an abnormally and persistently increased goal-directed activity. The patient must also have three of the following symptoms (four if mood is irritable): inflated self-esteem or grandiosity, decreased need for sleep, pressured speech, flight of ideas, distractibility, increased hyperactivity or psychomotor agitation, and involvement in high-risk activities without respect to the consequences. A hypomanic episode is a milder form of mania. This episode must exist for 4 days or longer and is not severe enough to warrant hospitalization, is not severe enough to cause marked social or occupational impairment, and is not associated with psychosis.
    2. The *DSM-5-TR* includes two types of bipolar disorder (I and II):
        a. Bipolar I: Chronic disorder marked by one or more manic or mixed episodes. Although major depressive episodes are not necessary for the diagnosis, most patients have depressive episodes.
        b. Bipolar II: Chronic disorder marked by one or more major depressive episodes, accompanied by at least one hypomanic episode
        c. Cyclothymic disorder: Several periods of hypomania and mild depression, none of which meet the criteria for mania or major depressive episode
        d. Rapid cycling: At least four episodes of mania, hypomania, or depression in 1 year with 2 months between episodes or a switch to the opposite polarity

3. Bipolar disorder, particularly type II bipolar disorder, is often misdiagnosed as major depression. The diagnosis is important because the two conditions are treated differently.

B. Lithium for Bipolar Disorders
   1. The exact mechanism of action for lithium is unknown, but it appears to be neuroprotective.
   2. Lithium continues to be the gold standard for treating type I bipolar disorder. Lithium is effective for the manic and depressive components. Although lithium is not a particularly good antidepressant as monotherapy in unipolar depression, it is effective in patients with bipolar disorder. Lithium has evidence for reducing suicidality when used for bipolar disorder.
   3. Antimanic effects can occur in 1–2 weeks. Most clinicians use antipsychotics or benzodiazepines as adjunctive therapy during this period to cover the agitation and other symptoms. Antidepressant effects may take 6–8 weeks.
   4. Pharmacokinetics: Lithium's half-life is 20–24 hours. Lithium is excreted 95% unchanged by glomerular filtration, and anything that alters the glomerular filtration rate affects its clearance. Pharmacokinetic methods are available for early prediction of doses, but waiting 5–6 days for steady state seems to work just as well.
   5. Initial dosing is 600–900 mg/day in divided doses, and dosing is then titrated according to response and tolerability. Maintenance doses are based on serum concentrations, symptom relief, and the occurrence of adverse effects.
   6. A pre-lithium workup includes a complete blood cell count, electrolytes, renal function, thyroid function tests, urinalysis, ECG, and pregnancy test for women of childbearing age.
   7. Monitoring: Serum concentrations must be monitored. Most clinicians will aim for concentrations of 0.8–1.2 mEq/L in acute mania and 0.6–1.0 mEq/L during maintenance. Concentration-response data are based on 12-hour postdose concentrations, so concentrations should be ordered in the morning 12 hours after the last evening dose. Renal function tests, thyroid function tests, and a urinalysis should be done every 6–12 months.
   8. Adverse effects are common with lithium, particularly during therapy initiation or after dose changes. Table 10 lists common adverse effects.
   9. Symptoms of lithium toxicity include lethargy, coarse tremor, confusion, seizures, and coma and may even result in death. Patients who present to urgent care on lithium therapy should always be monitored for lithium toxicity before any medication adjustments. Lithium concentration and sodium/renal function should be obtained so that lithium concentrations can accurately be estimated. Treatment of choice for severe lithium toxicity is hemodialysis.

Table 10. Adverse Effects Associated with Lithium

Problem	Potential Interventions
Rash or ↑ psoriasis	Discontinue the drug temporarily or permanently
Tremor	Reduce dose; add β-blocker
CNS toxicity (e.g., agitation, confusion)	Reduce dose
GI (nausea, vomiting, diarrhea)	Reduce dose; try ER product, split doses
Hypothyroidism	Give levothyroxine; discontinue lithium, if necessary
Polydipsia or polyuria	Reduce dose, manage fluid intake; single bedtime dosing helps
Interstitial fibrosis, glomerulosclerosis	Keep dose at lowest effective concentration; avoid dehydration
Teratogenicity	Avoid during first trimester, if possible

CNS = central nervous system; ER = extended release.

10. Pregnancy: Lithium passes the placental barrier and has been associated with cardiac and other abnormalities, including Ebstein abnormality when taken during the first trimester. However, it may have a lower risk than previously thought. Women of childbearing age should be counseled on its potential effects. Risks of discontinuing lithium therapy must be weighed against potential effects on the fetus when making decisions regarding lithium therapy during pregnancy.
11. Table 11 lists additional situations to consider during lithium therapy.

Table 11. Situations to Consider During Lithium Therapy

Situation	Factors	Results
Drug interactions	Diuretics	
	Thiazides	↑ Li Cp; avoid use to reduce toxicity
	Furosemide	↑ Li Cp; avoid use to reduce toxicity
	Amiloride	Little effect
	NSAIDs	↑ Li Cp; avoid use to reduce toxicity
	Theophylline	↓ Li Cp
	ACEIs	↑ Li Cp; avoid use to reduce toxicity
	Neuromuscular blockers	Li prolongs action
	Neuroleptics	Li may potentiate EPS
	Carbamazepine	↑ CNS toxicity
Thyroid	Li ↓ synthesis and release of thyroid hormone	Hypothyroidism
Pregnancy	↑ GFR	↓ Li Cp (first and second trimesters; third trimester may return to baseline)
Aging	↓ GFR	↓ Li requirements
	↑ Sensitivity to ADRs	Li toxicity
↓ Renal function	↓ GFR, ↑ creatinine and BUN	↑ Li Cp
Dehydration, salt restriction, and extrarenal salt loss	↑ Sodium reabsorption	↑ Li Cp

ACEI = angiotensin-converting enzyme inhibitor; ADR = adverse drug reaction; BUN = blood urea nitrogen; ; CNS = central nervous system; Cp = plasma concentration; EPS = extrapyramidal symptoms; GFR = glomerular filtration rate; Li = lithium; NSAID = nonsteroidal anti-inflammatory drug.

C. Antiseizure medications for Bipolar Disorder: These are also considered mood-stabilizing drugs that reduce manic and depressive episodes. See the Neurology chapter for additional drug-specific details.
   1. Divalproex/valproic acid (Depakene, Depakote, Depacon, Stavzor):
      a. As effective as lithium in acute and prophylactic management. Divalproex appears to be good for bipolar disorder with rapid cycling but may not be as effective during depressive episodes. Divalproex is also beneficial for patients with dysphoric mania, mixed episodes, or a history of SUD.
      b. Boxed warnings:
         i. Hepatotoxicity: Can result in death. Most common during the first 6 months of therapy. Risk is higher in children younger than 2 years. Liver function tests should be monitored routinely at the start of therapy and routinely thereafter, particularly during the first 6 months.
         ii. Mitochondrial disease: Patients with mutations of the mitochondrial DNA polymerase gamma (*POLG*) gene, such as Alpers-Huttenlocher syndrome, are at an increased risk of valproate-induced liver failure and death. Valproate is contraindicated in these patients.

iii. Fetal risk: Valproate can cause major congenital malformations, particularly neural tube defects (including spina bifida), decreases in IQ scores, and neurodevelopmental disorders after in utero exposure. Valproate should not be used in women of childbearing age unless other medications have failed to provide adequate therapeutic benefit. Women of childbearing age who are taking valproate should also be receiving effective contraception.

iv. Pancreatitis: Life-threatening pancreatitis can occur but is uncommon (less than 5%). Life-threatening pancreatitis can recur with reinitiation of valproate, so valproate should not be reinitiated.

c. Reference serum concentrations are 50–125 mcg/mL, but the exact concentration necessary for therapeutic effect is not well established. Serum concentrations should be interpreted in connection with clinical response. Therapeutic effects are usually seen with doses of 10–20 mg/kg/day. The trough serum concentration can be checked 3–5 days after initiation or a change in dose. Hypoalbuminemia increases the risk of increased free concentrations. Treatment nonresponse is common if the dose is too low; however, the free fraction increases as the serum concentration is increased (above 100–125 mcg/mL). Dose-related adverse effects that occur at serum concentrations greater than 80 mcg/mL include neurotoxicity, sedation, hair loss, and thrombocytopenia. The ER preparation has lower bioavailability than the enteric-coated preparation. The dose should be increased by 8%–20% when converting to the ER product.

2. Carbamazepine (Tegretol, Tegretol XR, Equetro): Effective for acute mania and maintenance therapy, particularly in patients with a history of head injury. Equetro is FDA approved for acute manic and mixed episodes. The serum concentration does not correlate well with therapeutic effect; however, it can be used to monitor for adherence and toxicity. Carbamazepine can also be added to lithium for patients who have not responded to monotherapy, but this increases the risk of neurotoxicity (see Lithium section earlier) and is not commonly done in practice. As a reminder, carbamazepine is a strong inducer of CYP metabolism. Carbamazepine also autoinduces its own metabolism and thus can take time to come to steady state. See the Neurology chapter for more information.
3. Lamotrigine (Lamictal):
   a. Has been approved for maintenance therapy. Lamotrigine appears particularly effective in preventing future depressive episodes of bipolar disorder. Lamotrigine is less effective than other mood stabilizers for preventing the manic phase.
   b. A Stevens-Johnson rash occurs in about 0.3% of adults and 1% of children. Lamotrigine must be discontinued if a rash occurs and should never be rechallenged. Risk increases with rapid dose titrations, high doses, young age, and concurrent use of valproic acid. The rash is most common within the first 2–8 weeks of therapy. If the medication is missed for greater than 3–5 half-lives (about 5 days), it must be retitrated from the starting dose.
   c. The dose titration must be halved if lamotrigine is given with valproate and doubled if given with carbamazepine because of drug-induced alterations in lamotrigine metabolism. The titration period is lengthy, so the onset of therapeutic effect can be delayed. For this reason, lamotrigine is not helpful in the acute setting.
   d. Lamotrigine has been associated with aseptic meningitis in adult and pediatric patients. Patients who experience headache, fever, chills, nausea, vomiting, stiff neck, rash, abnormal sensitivity to light, drowsiness, or confusion while taking lamotrigine should contact their health care professional right away. In 15 of 40 identified cases of aseptic meningitis, symptoms returned when patients were rechallenged with lamotrigine. Symptoms have occurred 1–42 days after the drug was started, and many patients required hospitalization.

e. A rare but life-threatening immune reaction called hemophagocytic lymphohistiocytosis (HLH) can occur with lamotrigine. Onset is usually within the first few weeks of therapy. Symptoms may include fever, rash, hepatosplenomegaly, organ system dysfunction, and blood dyscrasias. Patients who develop this condition should be taken off lamotrigine and changed to alternative treatment.

4. Other antiseizure medications, including levetiracetam, oxcarbazepine, and topiramate, are used for bipolar disorder, but data regarding their efficacy are scarce. Data for gabapentin suggest it is ineffective.

D. Antipsychotics for Bipolar Disorder: Antipsychotics, particularly SGAs, have mood-stabilizing properties. Antipsychotics can be used alone or with anticonvulsant mood stabilizers to treat bipolar symptoms. Metabolic adverse effects associated with antipsychotic use should be considered when medications are administered long term (see the Schizophrenia section).

1. Acute treatment: Antipsychotics treat acute symptoms of mania, including aggression and irritation, and any co-occurring psychosis. Antipsychotics are often combined with a traditional mood stabilizer for severe symptoms. All SGAs have received FDA approval for use in acute mania or mixed episodes except for brexpiprazole, clozapine, iloperidone, lumateperone, and lurasidone. For acute mania, the Canadian Network for Mood and Anxiety Treatments/International Society for Bipolar Disorders (CANMAT/ISBD) guidelines include aripiprazole, asenapine, cariprazine, paliperidone (more than 6 mg daily), quetiapine, and risperidone among the first-line agents.
2. Bipolar depression: Cariprazine, quetiapine, lumateperone, and lurasidone are approved for bipolar depression. Olanzapine is also approved for bipolar depression when combined with fluoxetine. Data for aripiprazole suggest it is ineffective for bipolar depression.
3. Maintenance treatment: The LAI antipsychotic formulations Risperdal Consta and Abilify Maintena have been approved for use in bipolar maintenance as monotherapy. The CANMAT/ISBD guidelines also recommend olanzapine and quetiapine.

E. Dexmedetomidine for bipolar disorder: Similar to schizophrenia, dexmedetomidine can be used to treat acute agitation associated with bipolar disorder.

F. Benzodiazepines for Bipolar Disorder: Benzodiazepines are acutely helpful for agitation but not for the core symptoms, nor do they prevent relapses. Benzodiazepines are particularly useful for insomnia, hyperactivity, and agitation. Lorazepam or diazepam is often used in the acute setting. Long-term therapy is not recommended.

G. Antidepressants for Bipolar Disorder:

1. Use of antidepressants in bipolar disorder is controversial, given concern for switching to the manic phase, particularly in patients with type I bipolar disorder. The risk appears greater with TCAs and SNRIs (particularly venlafaxine) than with SSRIs or bupropion. Because individual patients with bipolar disorder may benefit from antidepressants, the ISBD stopped short of recommending against any use of antidepressants. However, antidepressants should not be used as monotherapy, and their use should be minimized in general. Antidepressants should not be used in bipolar depression if symptoms of mania are also present. The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) trials found no statistically significant increased episodes of depression in patients taking mood stabilizers who discontinued their antidepressants. Patients with bipolar disorder taking mood stabilizers who received either paroxetine or bupropion were no more likely to achieve remission or have a durable recovery than those receiving placebo. These patients were also no more likely to switch to a manic phase.
2. Fluoxetine in combination with olanzapine is approved to treat depression associated with type I bipolar disorder.

H. Type II Bipolar Disorder: The depressive phase tends to be more debilitating. Patients are usually functional during hypomanic episodes. Treatment therefore focuses on the depressive phase. Lithium is a first-line agent, but it may not achieve remission as monotherapy and takes time to relieve symptoms. Quetiapine is preferred for acute symptom treatment. Lurasidone can also be used. Lamotrigine is a reasonable alternative for longer-term symptom control, but because of its slow titration schedule, it is not useful in the acute setting. Other mood stabilizers can be used but may not be as efficacious as for type I bipolar disorder. Antidepressants are used more commonly but should be used with caution, and never as monotherapy. Olanzapine and fluoxetine may thus be an option.

Patient Cases

13. A recent Iraq war veteran has responded to treatment with paroxetine for major depression for the past 3 weeks. Clinical presentation today includes experiencing nightmares, "feeling on edge all the time," and having flashbacks of time in the war. After evaluation, the patient is diagnosed with posttraumatic stress disorder (PTSD). There is no history of substance dependence and no significant medical history. Which recommendation is most appropriate for this patient at this time?
    A. Continue paroxetine because it treats both PTSD and major depression.
    B. Discontinue paroxetine and initiate sertraline, which treats both PTSD and major depression.
    C. Continue paroxetine and add lorazepam for the anxiety symptoms.
    D. Discontinue paroxetine and initiate buspirone for the anxiety symptoms.

14. A 48-year-old has newly diagnosed generalized anxiety disorder (GAD). The patient cannot sleep at night and reports frequent headaches treated with ibuprofen. Family history is positive for depression (mother) and anxiety (sister). Which medication would be best for long-term symptom resolution?
    A. Alprazolam.
    B. Buspirone.
    C. Paroxetine.
    D. Pregabalin.

15. A 27-year-old with panic disorder is having difficulty functioning at work. The first panic attack occurred while getting a cup of coffee. It felt like a heart attack and was evaluated at the local emergency department, where physical causes were ruled out. There have been several subsequent episodes. Place and time of repeat episodes are unpredictable. Absenteeism from work is high, and job security is thus a concern. The medical history is otherwise unremarkable. Which medication would most quickly allow the patient to return to work?
    A. Alprazolam.
    B. Buspirone.
    C. Paroxetine.
    D. Venlafaxine.

16. A 21-year-old has newly diagnosed obsessive-compulsive disorder (OCD). They cannot hold a job because they are consumed by their obsessions and compulsions. They are convinced that their obsessions are reality. Which medication is most appropriate to initiate?
    A. Bupropion.
    B. Desipramine.
    C. Fluoxetine.
    D. Mirtazapine.

IV. ANXIETY AND RELATED DISORDERS

A. Overview of Anxiety Disorders
   1. Generalized anxiety disorder (GAD) is characterized by 6 months or more of excessive worry or anxiety, generally with an unidentified cause.
   2. Panic disorder is characterized by discrete periods of sudden, intense fear or terror and feelings of impending doom. This is followed by continued worry about the implications of the panic attacks. Usually, the precipitating cause is unknown, but the patient can become conditioned to believe it is attributable to some environmental cause.
   3. Agoraphobia: Intense fear in two or more settings (mostly in the open or in public). These settings include using public transportation, being in open spaces, being in enclosed spaces, standing in line or being in a crowd, and being outside the home alone.
   4. Social anxiety disorder is characterized by marked and persistent fear and anxiety in social or performance situations that are recognized as excessive or unreasonable. These situations are either avoided or endured with intense anxiety.
   5. Specific phobias are characterized by intense fear or anxiety induced by a specific object.
   6. Obsessive-compulsive disorder (OCD), which used to be classified as an anxiety disorder, now has its own designation. Obsessions are recurrent and persistent thoughts, urges, or images that are intrusive and unwanted (e.g., fear of contamination, doubts, need for symmetry). Compulsions are ritualistic behaviors (e.g., washing the hands, combing the hair, cleaning the house) that relieve anxiety from the obsessions.
   7. Posttraumatic stress disorder (PTSD), which also used to be classified as an anxiety disorder, has been moved to a category titled "Trauma- and Stressor-Related Disorders." PTSD follows a traumatic event. PTSD is characterized by increased arousal and avoidance of stimuli that approximate the original traumatic event.
   8. See the *DSM-5-TR* for more details on each specific disorder.

B. Pharmacotherapeutic Options for Anxiety and Related Disorders
   1. Benzodiazepines: These drugs have anxiolytic properties, and some have preventive efficacy for panic attacks. Benzodiazepines are not appropriate for all anxiety disorders (see the individual disorders for role). Depending on the agent, the onset can be quite rapid. The high-potency, short-half-life agents are the most rapid acting. They are effective for treating the acute somatic and autonomic symptoms of anxiety but do not adequately address the underlying cognitive and psychological pathology.
      a. Pharmacologically, benzodiazepines share, to various degrees, five properties: (1) anxiolytic, (2) hypnotic, (3) muscle relaxation, (4) anticonvulsant, and (5) amnesic actions. Tolerance of the anxiolytic action is uncommon. Benzodiazepines are differentiated by their half-life (plus or minus active metabolites) and potency.
         i. Table 12 compares the half-lives and equivalent doses of the five main/most commonly prescribed benzodiazepines for anxiety disorders.

Table 12. Half-lives and Equivalent Doses of the Most Commonly Prescribed Benzodiazepines

Agent	Half-Life (hr)	Equivalent Dose (mg)
Alprazolam (Xanax)	6–12	0.5
Chlordiazepoxide (Librium)	5–30[a]	25
Clonazepam (Klonopin)	20–50	0.5
Diazepam (Valium)	20–100[b]	10
Lorazepam (Ativan)	10–18	1

[a]Active metabolites: Desmethylchlordiazepoxide, demoxepam (half-life 14–95 hr), desmethyldiazepam (half-life 71–100 hr).

[b]Active metabolite: Desmethyldiazepam (half-life 71–100 hr).

b. Primary issues associated with benzodiazepines are tolerance and dependence. Tolerance of the hypnotic actions occurs within days. Dependence occurs within weeks to months of continued use. Abrupt cessation can lead to withdrawal and may be life threatening. Hence, it is generally recommended that treatment periods be restricted to 3–4 weeks, or about the time an antidepressant takes to begin working for anxiety symptoms. After this time, the patient is tapered off the benzodiazepine to avoid withdrawal symptoms. If the patient has taken the benzodiazepine for a significant time, it can take several months to more than 1 year to complete. In practice, many patients go on to use benzodiazepines for long periods. Often, these patients are not in remission, despite treatment with maintenance medications. Minimize use of benzodiazepines in patients with a history of SUD or risk factors for SUD because of the risk of misuse. Information on benzodiazepine tapers can be found at deprescribing.org.

c. Risks associated with concomitant use with opioids: Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of these drugs for patients in whom alternative treatments are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation. Both benzodiazepines and opioids carry a boxed warning to this effect.

2. Antidepressants: SSRIs are also effective for several anxiety disorders and are the agents of choice for long-term treatment of anxiety disorders. Venlafaxine has been approved for GAD and social anxiety disorder. Duloxetine is also approved for GAD. Some initial symptoms may be improved within days, but the full benefit of treatment may take weeks, as for depression treatment. TCAs have preventive efficacy for panic disorder and anxiolytic activity. About 25% of patients with anxiety disorders (particularly GAD and panic disorder) have a hyper-stimulatory response to antidepressants, which can be confused with a worsening of the anxiety symptoms. This response is more common when therapy is first begun. Using low doses at first can help. Antidepressants can also help with anxiety that accompanies depression. Therapeutic doses are generally higher for almost all anxiety disorders (except social anxiety disorder) than for depression.
3. Buspirone: This drug has anxiolytic properties, but clinicians are divided on its real value in treating GAD. Buspirone has little efficacy for other anxiety disorders. The main drawback to buspirone is its long onset of action (weeks). In the meantime, the anxiety must be covered with another agent. Some clinicians use short-term benzodiazepines as a bridge until buspirone takes effect. Buspirone must also be dosed two or three times daily as scheduled, which decreases the chances for adherence. Buspirone should only be scheduled and never used as needed.
4. Miscellaneous agents
   a. β-Blockers are sometimes used to block the peripheral symptoms of panic disorder or performance anxiety.
   b. MAOIs can be effective for panic disorder when the patient also has atypical depression. However, MAOIs are seldom used because of the potential for serious adverse effects.
   c. Antihistamines with sedating properties (e.g., hydroxyzine) can help reduce physical symptoms of anxiety.
   d. Barbiturates are seldom used. They are often less effective and can be lethal if taken in overdose.
   e. Antipsychotics are not considered first-line agents for anxiety disorders. Selected SGAs can be useful add-on therapy for OCD, GAD, and PTSD.
5. CBT should be an integral part of any therapeutic plan for anxiety disorders.

C. Recommended Therapy for Specific Anxiety and Related Disorders
   1. GAD
      a. Antidepressants: These are considered first-line agents. Evidence is strongest for the SSRIs (escitalopram, paroxetine [IR and CR], and sertraline) and the SNRIs (duloxetine and venlafaxine XR), all of which are FDA approved for the indication.

b. Benzodiazepines: This class of drugs is rapidly effective; if possible, try to discontinue in 3–4 weeks or once the patient has remittance of symptoms. Benzodiazepines are more effective against somatic symptoms than against the underlying pathology. Evidence is strongest for alprazolam, diazepam, and lorazepam.
c. Buspirone: Can be considered when benzodiazepines should be avoided (e.g., in patients with a history of SUD); takes 2–4 weeks to be effective. Buspirone is considered a second-line agent.
d. Pregabalin: Depending on the guidelines, it is considered a first- or second-line agent (behind antidepressants). Does not carry an FDA indication for treating any form of anxiety. Limited data suggest similar efficacy with venlafaxine and benzodiazepines. Pregabalin can also be used as an adjunct.
e. Not effective: β-Blockers
f. CBT or another type of psychotherapy should be included with pharmacotherapy.
g. In treatment-refractory patients, augmentation with aripiprazole, quetiapine, olanzapine, or risperidone can be tried.

2. Panic disorder
   a. Antidepressants: First-line therapy. These include all the SSRIs and venlafaxine XR, all of which carry FDA approval.
   b. Benzodiazepines: High-potency agents; effective; rapid onset; evidence is strongest for alprazolam, clonazepam, diazepam, and lorazepam
   c. Not effective: Buspirone, β-blockers, antihistamines, trazodone. Bupropion is considered third line in some guidelines and is not recommended in others.
   d. CBT and other psychotherapies are effective.
   e. Patients with panic disorder tend to have a higher sensitivity to physical adverse effects. For this reason, these patients should be initiated on low doses of antidepressants – as low as 25 mg of sertraline or 10 mg of paroxetine. If the patient decides to stop antidepressant therapy, tapering should be very slow to minimize rebound panic symptoms.
3. OCD
   a. Serotonergic agents are effective – SSRIs (escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline). Depending on guidelines, clomipramine is considered a first- or second-line agent. Because of its adverse effect profile, clomipramine is typically used clinically as second line. Patients tend to require doses of antidepressants at the higher end of the dosing range.
   b. CBT is as effective as pharmacotherapy and is considered the treatment of choice for adolescents and adults with mild OCD.
   c. Alone, SSRIs often fail to control OCD completely. Not many other drugs help. Augmentation with haloperidol or an SGA (aripiprazole, olanzapine, quetiapine, or risperidone) may help. In general, high antipsychotic doses need to be used.
4. PTSD
   a. PTSD can be combat or non–combat related, and response to therapy may vary depending on the source of trauma.
   b. Psychotherapy is considered the cornerstone of treatment. Effective methods incorporate CBT, including exposure therapy and trauma-based cognitive processing therapy.
   c. Medications are considered adjuncts to psychotherapy. They are preferred if psychotherapists are not readily available or if a patient declines psychotherapy.
   d. SSRIs (sertraline and paroxetine are FDA approved, but evidence is also strong for fluoxetine) and venlafaxine XR are considered first-line agents.
   e. Augment with other agents to treat specific symptoms.
      i. Prazosin is commonly used for PTSD-associated nightmares, though evidence on its efficacy is conflicting.
      ii. Antiseizure medications can be used for aggression, anger, and depression (carbamazepine, lamotrigine, topiramate). Valproic acid is not considered effective.

iii. SGAs can be used for psychotic symptoms (aripiprazole, quetiapine, risperidone). Some guidelines recommend against the use of olanzapine because of its high incidence of metabolic syndrome.

f. Benzodiazepines are sometimes used acutely for sleep disturbances, but use should be very limited. Most data analyses indicate a lack of efficacy. Benzodiazepines have dissociative and disinhibiting properties and may worsen non-hyperarousal symptoms. Benzodiazepines may also interfere with the trauma recall (secondary to memory impairment) and fear-conditioning aspects of psychotherapy. The Veterans Affairs/Department of Defense (VA/DoD) guidelines recommend against the use of benzodiazepines.

5. Social anxiety disorder
   a. CBT is the most important modality.
   b. Antidepressants: First-line medication for treatment; SSRIs (paroxetine [IR and CR] and sertraline are FDA approved, but evidence also supports the use of escitalopram, fluvoxamine [IR and CR]), and venlafaxine XR (FDA approved). Response to antidepressants tends to be slow (up to 12 weeks) and has a flat dose-response curve (lower antidepressant doses are needed).
   c. Benzodiazepines (alprazolam and clonazepam) are considered second-line agents, but use should be minimized, given the risk of SUDs among patients with social anxiety disorder.
   d. Antiseizure medications: Pregabalin is considered a first-line agent, and gabapentin is a second-line agent.
6. Specific phobias
   a. Not treated with medication
   b. Systematic desensitization and other behavioral approaches often effective

Patient Case

Questions 17–19 pertain to the following case.

A 38-year-old kindergarten teacher presents to the clinic today with noticeable dark circles under the eyes. They have difficulty with sleep, mainly with staying asleep. It takes about 20 minutes to fall asleep, but after about 5 hours, they wake up and cannot fall asleep again for several hours. This pattern has negatively affected job performance, and they feel tired all the time. They once took diphenhydramine for sleep but had to miss work because of extreme drowsiness in the morning. They wonder whether they could take any other medications. Other medical problems include hypothyroidism (levothyroxine 125 mcg at bedtime), hypertension (hydrochlorothiazide 25 mg in the morning), chronic back pain (ibuprofen 800 mg three times daily), and MDD (citalopram 20 mg in the morning).

17. Which agent is most likely contributing to insomnia?
    A. Citalopram.
    B. Hydrochlorothiazide.
    C. Ibuprofen.
    D. Levothyroxine.

18. Which medication used for insomnia is most appropriate to recommend for this patient after adjusting the medication in question 17?
    A. Trazodone.
    B. Temazepam.
    C. Zaleplon.
    D. Zolpidem.

Patient Case *(Cont'd)*

19. Which adverse effect of zolpidem would carry the greatest potential for harm in this patient?
    A. Orthostasis.
    B. Disorientation.
    C. Abnormal behaviors while asleep.
    D. Seizures with high doses of the drug.

V. INSOMNIA

A. Normal Sleep Patterns and Neurochemistry/Physiology of Sleep
    1. About one-third of a life is spent in sleep. Optimal sleep duration for most adults to maintain good health is 7–9 hours per 24-hour period. Variation exists among individuals and according to age.
    2. Adverse outcomes, including increased mortality, are associated with both short sleep duration (6 hours or less per 24-hour period) and long sleep duration (more than 9–10 hours per 24-hour period).
    3. The body's circadian rhythm is controlled by both internal and external factors. It sets the sleep-wake cycle at 24.2 hours, which is modified by sensory input (e.g., darkness to signal sleep and brightness to signal wakefulness). The suprachiasmatic nucleus (SCN) is the main control center for sleep, and the retinal ganglion cells send direct signals to the SCN to provide information about light.
    4. The neural networks regulating sleep-wake cycles are located in the brain stem, basal forebrain, and hypothalamus, with projections to the cortex and thalamus.
    5. The reticular activating system maintains wakefulness, and when activity here declines, sleep occurs.
    6. Several neurotransmitters are involved in the sleep-wake cycle. Norepinephrine, acetylcholine, histamine, orexin, and serotonin promote wakefulness. γ-Aminobutyric acid (GABA), adenosine, and melatonin promote sleep.
    7. Sleep is divided into two categories: rapid eye movement (REM) and non-REM (see Table 13). They can be characterized by measurements with simultaneous electroencephalograms, electro-oculograms, and electromyograms. These are used to measure sleep latency (time to sleep onset), number of awakenings, number of stage shifts during the night, and latency to REM. These recordings are called polysomnography. Polysomnography is not a routine part of diagnosing insomnia.

Table 13. American Academy of Sleep Medicine Sleep Stages

State	Characteristics	Purpose
Non-REM stage		Rest and rejuvenation
N1	Relaxed wakefulness	Initiate sleep
N2	Muscle atonia, low-voltage brain waves; alpha wave activity; low-voltage EEG with sleep spindles and K-complexes	
N3	Slow-wave (delta) activity	Deep sleep; restorative sleep
REM sleep	Low-voltage, mixed-frequency EEG; low muscle tone; REMs; autonomic fluctuations in heart rate and perspiration; and dreaming reported in 80%–90% of subjects	Unknown

EEG = electroencephalogram; REM = rapid eye movement.

8. Sleep architecture is cyclic and dynamic. Passing from wakefulness to stage 4 non-REM sleep takes about 45 minutes in young adults. REM usually occurs within 90 minutes of falling asleep; at first, REM lasts 5–7 minutes, but it becomes progressively longer through the night. The sleep cycle (non-REM stages 1–4 and REM), which lasts about 70–120 minutes, is repeated four to six times a night.
9. Sleep patterns change with age. Older adult patients experience less delta sleep, REM sleep, and total sleep time. They have more nocturnal awakenings and more total wake time at night. The incidence of insomnia may be as high as 40%.

B. Sleep Disorders
   1. The *DSM-5-TR* recognizes 10 sleep-wake disorders or disorder groups. Among the most common are insomnia disorder, hypersomnia disorder, narcolepsy, breathing-related sleep disorders (including sleep apnea), and parasomnias (including non-REM sleep arousal disorders such as sleepwalking type or nightmare disorders, and restless legs syndrome).
   2. Insomnia occurs in 35%–50% of the adult population. Risk factors include increasing age, female sex, comorbid disorders (medical, psychiatric, sleep, and SUD), shift work, and possibly unemployment and lower socioeconomic status. The course is often chronic, with persistence of one to several years in 50%–85% of people.
   3. Insomnia has a reciprocal relationship with other psychiatric diagnoses. Many patients with insomnia have comorbid anxiety disorders, mood disorders (including depression and bipolar disorder), psychotic disorders (schizophrenia and schizoaffective disorder), dementia, attention deficit disorder, or personality disorders. Insomnia can also be a symptom of psychiatric disorders such as anxiety, depression, and bipolar disorder and can exacerbate or precipitate episodes.
   4. Insomnia causes significant morbidity, including impaired driving and occupational accident risk.
   5. Insomnia disorder (*DSM-5-TR*)
      a. Dissatisfaction with sleep quantity or quality, associated with one or more of the following symptoms:
         i. Difficulty initiating sleep (also called onset or initial insomnia)
         ii. Difficulty maintaining sleep, characterized by frequent awakenings or problems returning to sleep after awakenings (also called sleep maintenance or middle insomnia)
         iii. Early morning awakening with an inability to return to sleep (also called late insomnia)
      b. The sleep disturbance causes clinically significant distress or impairment in one or more important areas of function in life.
      c. The sleep difficulty occurs at least 3 nights of the week.
      d. The sleep difficulty is present for at least 3 months.
      e. Occurs despite the opportunity for adequate sleep
      f. The insomnia is not better explained by another sleep-wake disorder or comorbid mental or physical condition and is not attributable to the effects of a substance.
      g. Evaluation of insomnia should include an assessment of medical and psychiatric status. Medical causes are many and include disorders of the heart and lungs, disorders of the musculoskeletal system, diabetes, thyroid disease, and therapy with medications that can interfere with sleep. A detailed sleep history should be obtained that should include an evaluation of nighttime sleep, daytime functioning, sleep-wake rhythms, the sleeping environment, beliefs about sleep, and development of the sleep problem.
   6. Parameters used to monitor sleep
      a. Sleep onset latency (SOL) or time to sleep onset (TTSO): Time that it takes to transition from wakefulness to sleep
      b. Total sleep time (TST): Total sleep period (time in bed) minus the time spent awake
      c. Wake time after sleep onset (WASO): Time spent awake after initial sleep onset until awakening
      d. Sleep efficiency: Ratio of TST divided by the time spent in bed; reported as a percentage

7. Treatment goals
    a. Primary
        i. Improved sleep quality and time
        ii. Improved insomnia-related daytime impairments
    b. Other goals:
        i. SOL less than 30 minutes
        ii. WASO less than 30 minutes
        iii. Decreased frequency of awakenings
        iv. TST greater than 6 hours
        v. Sleep efficiency greater than 80%–85%
        vi. Formation of positive and clear association between the bed and sleeping
        vii. Improvement in sleep-related psychological distress
8. Nonpharmacologic management of insomnia
    a. CBT for insomnia (CBT-I) is considered the gold standard of therapy and is first line in many insomnia guidelines. CBT-I combines cognitive therapy with behavioral treatments, such as stimulus control and sleep restrictions, with or without relaxation therapy. For insomnia, the cognitive therapy portions work with the patient to identify maladaptive behaviors and cognitions that contribute to the patient's insomnia, bring the associated cognitive distortions to the patient's attention, and work with the patient to structure the thoughts into more sleep-compatible forms. CBT-I requires a trained professional and thus may not be available to all patients.
    b. Stimulus control is designed to extinguish the negative associations between the bed and undesired outcomes. The objective is to form a positive relationship between the bed and sleep and to foster a stable sleep-wake schedule. It involves the following:
        i. Go to bed only when sleepy.
        ii. Maintain a regular sleep schedule.
        iii. Avoid naps.
        iv. Use the bed only for sleep or sexual activity.
        v. If unable to fall asleep (or back to sleep) within 20 minutes (perceived, not by watching the clock), get out of bed, engage in a relaxing activity until drowsy, and then return to bed; repeat as necessary
    c. For all types of insomnia, patients can be instructed about good sleep hygiene in conjunction with stimulus control. These principles include:
        i. Maintain regular bedtimes and awakenings.
        ii. Sleep long enough to avoid feeling tired, but no more.
        iii. Optimize the bedroom conditions (e.g., light, temperature, removal of animals, minimize noise or use white noise).
        iv. Exercise regularly early in the day, but avoid vigorous exercise in the evening.
        v. Develop a bedtime ritual (at least 30 minutes) that allows you to unwind.
        vi. Have a light snack or beverage before bed, if hungry, but avoid heavy meals or spicy food.
        vii. Avoid stimulants such as caffeine and nicotine throughout the day, but particularly in the afternoons and evenings.
        viii. Avoid alcohol because it can lead to "fragmented" sleep.
        xi. Cover the clock or phone to minimize the risk of focusing on it throughout the night.
        x. Disconnect electronics and avoid light-emitting devices (e.g., television, phones, tablets, and computers) for at least 5–10 minutes before bed.
        xi. Ensure adequate exposure to natural light during the day.

C. Pharmacotherapy of Insomnia
   1. Pharmacotherapy works best for insomnia when it is part of an overall plan to deal with the causes and is used for well-defined periods. Initial treatment for 2–4 weeks may be appropriate, with a reevaluation of the continued need for treatment. Some patients with chronic insomnia may be appropriate candidates for longer therapy durations, though evidence for long-term use of medications is sparse. Little empiric evidence exists to guide treatment. If hypnotic medications are used long term, regular follow-ups should be scheduled at least every 6 months to monitor use. If a hypnotic is used long term, it should be tapered, not discontinued abruptly. Guidance for deprescribing hypnotics can be found at deprescribing.org.
   2. Agents that can depress respiration should be avoided in patients with respiratory disorders, a history of SUD, or obstructive sleep apnea.
   3. In the past, barbiturates were used as hypnotics. They are no longer indicated because of the risk of respiratory depression, with no respiratory depression ceiling.
   4. Benzodiazepines
      a. In general, they are safe, effective, and well tolerated by most patients, but they are not considered first line. Although all members of this class can be used as sedatives, only five are FDA approved and marketed as such. These five are primarily used as sedative-hypnotics because they are rapidly absorbed and produce CNS actions more quickly than most anxiety agents. Table 14 lists the sedative-hypnotic benzodiazepines. They are primarily differentiated by their onset of action, metabolism, and half-life in the body. According to their half-life, they are classified as short acting (half-life less than 6 hours), intermediate acting (half-life 6–24 hours), and long acting (half-life more than 24 hours). These are important parameters when selecting therapy. For instance, someone with problems falling asleep would probably benefit from an agent with a quick onset but short duration of action. Someone with problems maintaining sleep in the middle of the night might respond better to a drug with a longer half-life.

Table 14. Benzodiazepines for Insomnia

Drug (trade)	Usual Dose (mg)	Half-Life (hr)	Duration
Triazolam (Halcion)	0.125–0.25	2–6	Short
Temazepam (Restoril)	15–30	8–20	Intermediate
Estazolam (Prosom)	1–2	8–24	Intermediate
Flurazepam (Dalmane)	15–30	48–120	Long
Quazepam (Doral)	7.5–15	48–120	Long

      b. Benzodiazepines are usually well tolerated. However, several problems still exist.
         i. Tolerance: Tolerance can develop, particularly when the drugs are used consistently for long periods. These drugs are not indicated for chronic use; however, newer evidence is emerging that they may be effective for longer periods than originally thought. Most are effective for 2–4 weeks and, in some cases, longer. An intermittent pattern of use can reduce the development of tolerance.
         ii. Residual daytime sedation: This is a common concern of patients using these drugs and is especially likely with agents having a long half-life. Dose is also an important factor; always use the lowest effective dose.
         iii. Rebound insomnia: This can occur when the drug is discontinued abruptly. Insomnia is usually worse than at baseline and usually lasts for 1–2 days; tapering the drug may minimize its effect. Rebound insomnia is most common after the use of short- and intermediate-acting agents.
         iv. Anterograde amnesia: All benzodiazepines appear to impair the acquisition and encoding of new information. They may also impair memory storage and recall. Incidence may be dose-dependent.

v. Special populations: Be careful when using benzodiazepines in older adult patients because benzodiazepines can cause memory problems, increase the risk of falls, and accumulate (agents with a long half-life). If a benzodiazepine is used in this population, temazepam is preferred because of its phase II metabolism. Idiosyncratic reactions can occur in older adult and pediatric populations with benzodiazepine use.

vi. Withdrawal: Physical dependence will occur if these agents are used for more than 2–4 weeks. Symptoms of withdrawal include worsening insomnia, anxiety, muscle twitches, photophobia, tinnitus, auditory and visual hypersensitivity, and seizures. Minimize by gradually tapering the drug at discontinuation. Guidelines for deprescribing benzodiazepine and benzodiazepine receptor agonists in patients with insomnia are available (Can Fam Physician 2018;64:339; see also deprescribing.org), which recommend a slow taper.

D. Nonbenzodiazepine Receptor Agonists (Z-drugs)

1. Eszopiclone (Lunesta): This nonbenzodiazepine is a $GABA_A$ agonist whose half-life is 6 hours; thus, morning effects can result if it is taken late in the night. Eszopiclone can be used for chronic insomnia. The FDA reduced the starting dose to 1 mg to minimize next-day impairment. Patients should be counseled to use caution when driving or performing activities that require alertness, particularly with the 2- to 3-mg doses. Eszopiclone should be taken immediately before bed and when the patient will be in bed for at least 7–8 hours. Eszopiclone can cause a metallic taste in the mouth.
2. Zaleplon (Sonata): This is a nonbenzodiazepine with a pharmacology similar to zolpidem (see the text that follows) and a very short half-life. For patients with sleep maintenance problems, it may not last as long. However, zaleplon has a shorter half-life (about 1 hour) and may cause fewer problems in the morning, especially if given late. Zaleplon shortens onset to sleep but does not prolong sleep time or decrease the number of awakenings. Zaleplon is indicated only for short-term treatment of insomnia and has been used in trials for up to 5 weeks.
3. Zolpidem (Ambien): This nonbenzodiazepine sedative-hypnotic modulates the $GABA_A$ receptor complex.
   a. Compared with benzodiazepines, zolpidem lacks anticonvulsant action, muscle-relaxant properties, and respiratory depressant effect; it also has a lower risk of tolerance and withdrawal. Zolpidem should still be avoided in obstructive sleep apnea. Zolpidem is a good choice for patients in whom benzodiazepines should be avoided.
   b. Zolpidem is available as an IR tablet, CR tablet (Ambien CR), sublingual tablet (Edluar, Intermezzo), and sublingual spray (Zolpimist). The pharmacokinetics and indications vary depending on the dosing form. The sublingual spray has a shorter onset of action, but that of the sublingual tablet is similar to both the IR and the CR tablets.
   c. Indications vary by dosage form. All are indicated to decrease sleep latency. The CR tablets are indicated to improve sleep maintenance and can be used for longer-term therapy. The sublingual tablet formulation Intermezzo, but not Edluar, is indicated as an "as-needed" treatment for patients who have difficulty falling back to sleep as long as 4 hours or more of sleep remain.
   d. The FDA has reduced the dosing recommendations to limit next-day impairment. Dosing differs on the basis of the patient's sex and degree of debility. For women, the nightly dose is 5 mg (IR) or 6.25 mg (CR). For men, it is 5–10 mg (IR) or 6.25–12.5 mg (CR). Patients with debility and older adult patients should receive 5 mg (IR) or 6.25 mg (CR). Patients should be maintained on the lowest dose needed to benefit.
4. Patients should be warned about the potential risk of engaging in complex behaviors while asleep when taking sedative-hypnotics. Such behaviors may include driving, eating, having sex, or talking on the telephone while asleep (with amnesia for the event). Other cautions include anaphylaxis and decreased respiratory drive.

Table 15. Nonbenzodiazepines for Insomnia

Drug	Half-Life (hr)	Administration (minutes before sleep)	Indications			DEA Scheduling
			Sleep Onset	Sleep Maintenance	Chronic Therapy	
Daridorexant (Quviviq)	8	30	X	X		C-IV
Doxepin (Silenor)	Doxepin: 15.3 Nordoxepin: 31	30		X		Not controlled
Eszopiclone (Lunesta)	6	Immediately	X	X	X	C-IV
Lemborexant (Dayvigo)	17–19 (dose-dependent)	Immediately	X	X		C-IV
Ramelteon (Rozerem)	1–2.6	30	X		X	Not controlled
Suvorexant (Belsomra)	12	30	X	X		C-IV
Zaleplon (Sonata)	1	Immediately	X			C-IV
Zolpidem (Ambien)	1.4–6.5	Immediately	X	X (CR only)	X (CR only)	C-IV

DEA = Drug Enforcement Administration.

E. Orexin (OX1 and OX2) Receptor Antagonists
   1. The neuropeptide orexin promotes wakefulness. By blocking the OX1R and OX2R receptors, daridorexant (Quviviq), lemborexant (Dayvigo), and suvorexant (Belsomra) decrease sleep latency and promote sleep maintenance. Orexin receptor antagonists are contraindicated in patients with concomitant narcolepsy.
   2. All three orexin receptor antagonists should be taken with at least 7 hours of remaining sleep. Daridorexant and suvorexant should be taken within 30 minutes of bedtime. Time to onset may be delayed if taken with or immediately after food. Suvorexant may be administered with or without food.
   3. All three orexin receptor antagonists are substrates of CYP3A4. Daridorexant and lemborexant should be avoided in patients taking either inducers or inhibitors of CYP3A4. The dose of suvorexant must be decreased.

F. Miscellaneous Agents
   1. Doxepin (Silenor) is a TCA indicated for impaired sleep maintenance. Doses used are lower than for depression. Chances for morning effects are high because of the long half-life of both doxepin and its active metabolite, nordoxepin.
   2. Ramelteon (Rozerem): Melatonin agonist (no activity at the GABA or benzodiazepine receptor). Duration is 2–5 hours. To date, there is no evidence that this melatonin agonist is associated with dependence or tolerance, and it can be used long term for chronic insomnia. Ramelteon is primarily metabolized by CYP1A2, but inducers and inhibitors of CYP2C9 and CYP3A4 can also affect it. Ramelteon should be avoided in patients with severe sleep apnea. Melatonin, the molecule on which ramelteon is based, is available OTC as a dietary supplement. It is used off-label to treat jet lag and sleep onset insomnia.

3. Taking any of the agents listed in Table 15 with food can delay onset of effects, thus prolonging the time to onset of sleep and increasing the risk of hangover effects in longer-acting agents. Doxepin should be separated from meals by 3 hours.
4. OTC medications: These are most often antihistamines (doxylamine or diphenhydramine) that are both sedating and anticholinergic. They are possibly effective, but not as effective as benzodiazepines. Regular use is not recommended. In fact, some data suggest that they do not maintain efficacy beyond a few days. They are associated with a higher incidence of daytime sedation than short- or intermediate-acting benzodiazepines. Diphenhydramine has been popular when benzodiazepines were contraindicated. However, caution should be used in older adult patients because an anticholinergic action can cause delirium or worsen dementia or other medical conditions. In addition, diphenhydramine should not be administered with the cholinesterase inhibitors used for Alzheimer disease.
5. Other: In some situations, antidepressants such as trazodone can be used as sedative-hypnotics. These can be effective, and often, the dose required is lower than for depression. However, efficacy has not been fully established through clinical trials. Trazodone has been popular for managing insomnia caused by SSRI antidepressants (see discussion in Depression section). Trazodone is also popular by itself as a sleep agent because the potential for dependence is low. However, trazodone is associated with considerable adverse effects, and the data for long-term use are scant.

G. Guideline-Based Treatment (Chronic Insomnia)
   1. American Academy of Sleep Medicine (J Clin Sleep Med 2017;13:307-49)
      a. Initial (sleep onset) insomnia: Zaleplon, triazolam, ramelteon
      b. Middle (sleep maintenance) insomnia: Suvorexant, doxepin
      c. Sleep onset and maintenance insomnia: Eszopiclone, zolpidem, temazepam
      d. Recommends against: Trazodone, tiagabine, diphenhydramine, melatonin, tryptophan, valerian
      e. Inadequate data for other agents
   2. American College of Physicians (Ann Intern Med 2016;165:125-33)
      a. General population: Eszopiclone, zolpidem, suvorexant, doxepin
      b. Older adults: Eszopiclone, zolpidem, ramelteon, doxepin
   3. VA/DoD (available at https://www.healthquality.va.gov/guidelines/CD/insomnia/index.asp)
      a. Recommended: Doxepin, nonbenzodiazepine receptor agonist
      b. Insufficient evidence: Ramelteon, suvorexant
      c. Recommend against: Antipsychotics, benzodiazepines, chamomile, diphenhydramine, kava kava, melatonin, trazodone, valerian

Patient Cases

Questions 20–22 pertain to the following case.

A 50-year-old patient with a 25-year history of alcohol dependence was found unconscious after a drinking binge. The patient was first admitted to the medical unit for alcohol withdrawal symptoms before being transferred to the substance dependence unit. The last drink was 6 hours ago, and fluids have been initiated. The patient has had three alcohol withdrawal seizures in the past and an episode of delirium tremens. Significant hepatitis is also present, and liver function tests show AST 275 U/L and ALT 130 U/L. Additional laboratory test values include albumin 4.2 g/dL, alkaline phosphatase 152 IU/L, and γ-glutamyl transferase 470 units/L.

20. Which symptom are you most likely to observe in the medical unit in this patient on admission?
    A. Alcohol craving.
    B. Delirium tremens.
    C. Increased heart rate.
    D. Seizures.

Patient Cases (*Cont'd*)

21. Which agent is best for this patient's alcohol withdrawal symptoms?
    A. Chlordiazepoxide.
    B. Clonazepam.
    C. Diazepam.
    D. Lorazepam.

22. Which medication is best for this patient's alcohol dependence?
    A. Acamprosate.
    B. Diazepam.
    C. Disulfiram.
    D. Naltrexone.

23. A 34-year-old wants to stop using oxycodone. They have been buying it off the street and are using 160 mg daily. The patient has no interest in methadone maintenance but wants to enroll in an outpatient program. The last oxycodone dose was 24 hours ago. The patient is having some anxiety and muscle aches. Treatment will start in the clinic. Which is best to initiate in this patient?
    A. Buprenorphine 2 mg.
    B. Buprenorphine 4 mg.
    C. Buprenorphine/naloxone 2 mg/1 mg.
    D. Buprenorphine/naloxone 4 mg/1 mg.

VI. SUBSTANCE USE DISORDER

A. *DSM-5-TR* Criteria
    1. The *DSM-5-TR* recognizes a range of SUDs. Pharmacologic therapy is available for alcohol, opioid, and tobacco use disorders.
    2. General criteria for SUD: A pattern of use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:
        a. More of the substance is taken or the substance is taken longer than intended
        b. There is persistent desire or unsuccessful efforts to cut back or control use
        c. Much time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects
        d. Craving, or a strong desire or urge to use
        e. Recurrent use resulting in a failure to fulfill major obligations, such as at work, school, or home
        f. Continued use despite persistent or recurrent social or interpersonal problems caused by or exacerbated by the substance
        g. Because of substance use, the individual gives up or reduces important social, occupational, or recreational activities
        h. Recurrent use in situations in which it is physically hazardous
        i. Continued use despite knowledge of having a continued physical or psychological problem that is caused or exacerbated by use of the substance
        j. Tolerance, as evidenced by a need for more of the substance for the desired effect
        k. Withdrawal symptoms after a decrease in or discontinuation of use

B. Screening for SUD
   1. According to the Substance Abuse and Mental Health Services Administration (SAMHSA), all health care providers should screen for alcohol, tobacco, and other substance misuse (including opioids). Many validated tools exist for this purpose. A good review can be found in SAMHSA at https://store.samhsa.gov/product/TIP-63-Medications-for-Opioid-Use-Disorder-Full-Document/PEP20-02-01-006.
   2. Screening, brief intervention, and referral to treatment (SBIRT) model
      a. SBIRT is an evidence-based and universal approach to screening for SUD that is endorsed by SAMHSA. More information can be found at https://www.samhsa.gov/sbirt/about.
      b. SBIRT steps:
         i. Screening: Quickly assesses the severity of substance use and identifies the appropriate level of treatment
         ii. Brief intervention: Focuses on increasing insight and awareness regarding substance use and motivation toward behavior change
         iii. Referral to treatment: Those identified as needing more extensive treatment are provided with the appropriate access to specialty care.

C. SUDs are often comorbid with other psychiatric diagnoses.

D. Withdrawal from use of most substances of abuse is not life threatening, but can be distinctly uncomfortable. The exceptions to this are withdrawal from alcohol, benzodiazepines, and barbiturates, which are life threatening and should be undertaken with medical supervision.

E. Goal: Remission of the disorder, leading toward lasting recovery

F. SUD is a treatable chronic illness.

G. Treatment of SUD should be patient centered and use shared decision-making, motivational interviewing, and harm reduction strategies, as appropriate.

H. Alcohol
   1. CAGE questionnaire (for screening for alcohol use disorder)
      a. Questions:
         i. Have you ever felt you should **Cut** down on your drinking?
         ii. Have people **Annoyed** you by criticizing your drinking?
         iii. Have you ever felt bad or **Guilty** about your drinking?
         iv. Have you ever had a drink first thing in the morning to steady your nerves or to get rid of a hangover (**Eye-Opener**)?
      b. Scoring: 0 for each "no," 1 for each "yes." A score of 2 or more is a positive screen for problematic drinking. A score of 1 or more suggests the need for follow-up.
   2. Acute withdrawal
      a. Characteristic symptoms occur after alcohol discontinuation. The symptoms that develop, how quickly they develop, and the degree of severity depend on the level of alcohol use and a person's characteristics. Not all patients develop delirium tremens, nor do all develop seizures. These symptoms are difficult to predict, so detoxification should always be supervised. A history of alcohol withdrawal complications suggests that inpatient detoxification is indicated.

b. Table 16 lists the stages of acute alcohol withdrawal. Not everyone progresses through all stages.

Table 16. Stages of Acute Alcohol Withdrawal

Stage	**Onset** (after last drink or decrease in intake)	Symptoms
1	6–12 hr	Minor withdrawal symptoms: Agitation, anorexia, anxiety, diaphoresis, headaches, insomnia, nausea/vomiting, tachycardia, tremors
2	12–24 hr	Alcohol hallucinosis: Hallucinations – usually visual, but can be auditory or tactile (usually resolve within 48 hr)
3	24–48 hr	Withdrawal seizures (generalized tonic-clonic)
4	48–72 hr (peaks at 3–5 days)	Delirium tremens (alcohol withdrawal delirium): Agitation, diaphoresis, disorientation, hallucinations (usually visual), hyperpyrexia, hypertension, tremor

c. Delirium tremens, which can be life threatening, should be considered a potential medical emergency and treated promptly.

d. The seizures that occur are often difficult to control. Status epilepticus can develop; thus, it is important to ensure these patients have intravenous access before onset.

3. Treatment of acute alcohol withdrawal

a. The degree of symptoms and the resulting treatment level should be individualized, and an accurate history regarding amount, duration, and past withdrawal symptoms, including seizures and delirium tremens, should guide treatment.

i. Because of cross-tolerance at the $GABA_A$ receptors, benzodiazepines are considered first-line treatment for alcohol withdrawal symptoms, including delirium tremens and seizures.

ii. Chlordiazepoxide, clorazepate, diazepam, and oxazepam carry FDA indications for treating alcohol withdrawal, but other benzodiazepines are used off-label. Long-half-life benzodiazepines such as chlordiazepoxide and diazepam minimize the potential for breakthrough symptoms and allow for more self-taper between doses but may also lead to overmedication, particularly in older adult patients or patients with liver disease. Lorazepam or oxazepam is preferred in these patients. Lorazepam's shorter half-life allows for tighter control of dosing with minimal risk of oversedation.

iii. Several dosing regimens are used (Table 17). Symptom-driven treatment using the Clinical Institute Withdrawal Assessment for Alcohol scale (CIWA-Ar) is the gold standard. The CIWA-Ar consists of seven items and has a score range of 0–67. The higher the score, the more severe the symptoms. The patient's CIWA-Ar score is determined routinely. Patients are typically treated if the score is greater than 8–10 (depending on facility protocol). This protocol is efficacious and results in lower total benzodiazepine use.

iv. Scheduled dosing: For severe alcohol withdrawal, including in patients with a history of withdrawal seizures or delirium tremens, fixed-dose benzodiazepine therapy is used for 2–3 days, regardless of symptoms, with supplementation according to the CIWA-Ar score. The benzodiazepine can then be tapered for 3–4 days until symptoms have abated. The drawback of using scheduled dosing is the risk of overmedication. It is not appropriate for mild-moderate withdrawal, nor is this method commonly used for outpatient treatment.

v. Loading-dose (front loaded) protocol: Chlordiazepoxide is given at a dose of 25–100 mg every 1–2 hours until the withdrawal symptoms are alleviated (or CIWA-Ar is less than 10). Most patients will need two or three doses, especially those with a history of seizures during withdrawal, in which case three doses should be used. The half-life of chlordiazepoxide is long, and most patients will not need subsequent doses in this protocol once symptoms are relieved. Of course, patients should be monitored closely.

Table 17. Benzodiazepines for Acute Alcohol Withdrawal

Drug	CIWA-Ar Dosing	Fixed-Dose Regimen	Comments
Chlordiazepoxide (Librium)	25–100 mg PO	50 mg every 6–12 hr × 4; then 25 mg every 6 hr × 4; then 25 mg BID; then 25 mg at bedtime	Long acting; decrease dose for liver disease
Diazepam (Valium)	5–20 mg PO/IV/IM[a]	10 mg every 6 hr × 4; then 5 mg every 6 hr × 8	Decrease dose for liver disease
Lorazepam (Ativan)	2–4 mg PO/IV/IM	2 mg every 6 hr × 4; then 1 mg every 6 hr × 8	Preferred medication, particularly for older adults and those with liver disease; no active metabolites
Oxazepam (Serax)	10–30 mg PO	30 mg every 6 hr × 4; then 15 mg every 6 hr × 4	Short-acting; preferred in older adults and those with liver disease

[a]IM administration of diazepam is unreliable.

BID = twice daily; IM = intramuscular(ly); IV = intravenous(ly); PO = oral(ly).

b. Nutritional considerations
    i. Thiamine: Should be given to all patients to prevent Wernicke-Korsakoff syndrome. Because thiamine has poor oral bioavailability, it is administered intramuscularly/intravenously to replete thiamine in severe cases: 100–250 mg intramuscularly/intravenously daily for 3–5 days, followed by 100 mg by mouth three times daily for 1 week, and then 100 mg daily thereafter. Always give the first dose before glucose because thiamine is a cofactor for the metabolism of glucose.
    ii. Magnesium: Assess by serum chemistry; if low, give an intravenous supplement.
    iii. Electrolytes: Assess by serum chemistry, and add to intravenous solutions as indicated (e.g., potassium).
    iv. Vitamins: Patients are usually undernourished; a multivitamin and/or folic acid may be indicated.
    v. Fluid therapy: The patient may initially be overhydrated, but usually, fluid deficit will follow; replace fluids, usually with intravenous 5% dextrose solution with half-normal saline plus other electrolytes (e.g., potassium, phosphate).

c. Other agents: Antiseizure medications: as adjuncts to benzodiazepines in uncontrolled seizures. They should not be used as monotherapy for alcohol withdrawal seizures. Carbamazepine, gabapentin, and valproic acid have all been used. Of note, gabapentin does not decrease benzodiazepine requirements as assessed by CIWA-Ar in clinical studies.

4. Medications for alcohol use disorder
    a. Acamprosate (Campral) and naltrexone (Revia, Vivitrol) are considered first line.
    b. Naltrexone: This drug can also be used chronically and reduces cravings. If used, it should be combined with CBT. Naltrexone has a precaution listed for hepatocellular injury. Patients should have liver function tests monitored periodically. Naltrexone should be avoided in patients with acute hepatitis or severe hepatic impairment (liver function tests greater than 3 times the upper limit of normal). Additional adverse effects include nausea, diarrhea, injection site reactions, headache, insomnia, and nervousness. The ER injectable suspension (Vivitrol) is available in an intramuscular formulation and is approved for alcohol dependence in patients who can abstain from alcohol in an outpatient setting before treatment initiation. Naltrexone is also available as a daily oral tablet. For further details on use, see the naltrexone entry under Opioid Use Disorder in the text that follows.

c. Acamprosate (Campral): This drug is a structural analog of GABA that also reduces cravings. Evidence regarding efficacy is more mixed than with naltrexone. Acamprosate is not metabolized by the liver; however, it must be taken three times daily. The dose must be decreased for a CrCl of 30–50 mL/minute/1.73 m^2, and the drug should not be used in patients with a CrCl less than 30 mL/minute/1.73 m^2. It carries a warning for suicidal ideation and should not be used in patients with active suicidal ideation.

d. Disulfiram (Antabuse): This drug blocks aldehyde dehydrogenase. If alcohol is used with it, acetaldehyde concentrations increase. The person will develop symptoms that include nausea/vomiting, flushing, and headache, among others. For this reason, it is considered aversion therapy. Adherence is critical, and disulfiram is usually reserved for patients with considerable motivation for adherence. Caution should be exercised in patients with liver disease, particularly if it is severe or the patient has cirrhosis. Disulfiram has been associated with hepatotoxicity, though it is not known whether patients with existing liver disease are at an increased risk. Because of the increase in acetaldehyde concentrations, it should be avoided in patients with severe myocardial disease. It should not be combined with metronidazole because of an increased risk of encephalopathy. Patients should also be counseled to avoid alcohol-containing items, particularly medications and certain mouthwashes, because of the risk of adverse effects.

I. Opioid Use Disorder (OUD)
   1. Opioid-related overdose deaths, illicit use, and prescription misuse constitute a public health crisis.
   2. Opioid intoxication
      a. Symptoms include miosis (unless mydriasis occurs secondary to anoxia from overdose), together with one of the following signs beginning after opioid use: drowsiness or coma, slurred speech, or impaired attention or memory.
      b. Naloxone should be considered for all patients exposed to opioids regardless of the source. An excellent educational source is available at the AAPP (American Association of Psychiatric Pharmacists). https://aapp.org/guideline/naloxone. SAMHSA has an Opioid Overdose Prevention Kit available at https://store.samhsa.gov/product/Opioid-Overdose-Prevention-Toolkit/SMA18-4742. Repeat doses of naloxone are potentially necessary, depending on the potency of the opioid used. Naloxone should only be used in unresponsive patients beginning to show, or showing, signs of respiratory distress.
   3. Opioid withdrawal
      a. Not life threatening in the absence of concomitant medical conditions. See Table 18 for details.

Table 18. Timeline of Physical Signs of Opioid Withdrawal

Stage (after last use)	Grade	Physical Signs/Symptoms
Early withdrawal (symptoms may resemble mild flu)		
Short-acting opioids: 8–24 hr Long-acting opioids: ≥ 36 hr	1	Diaphoresis Insomnia Lacrimation, rhinorrhea, or both Restlessness Yawning
	2	Abdominal pain Arthralgia Mydriasis Muscle twitching Myalgias Piloerection

Table 18. Timeline of Physical Signs of Opioid Withdrawal (*Cont'd*)

Stage (after last use)	Grade	Physical Signs/Symptoms
Fully developed withdrawal		
Short-acting opioids: 24–72 hr Long-acting opioids: 72–96 hr	3	Anorexia or nausea Extreme restlessness Fever Hypertension Tachycardia Tachypnea
	4	Dehydration Diarrhea, vomiting, or both Fetal position Hyperglycemia Hypotension
Total duration: Short-acting opioids: 7–10 days Long-acting opioids: ≥ 14 days		

Adapted from: Substance Abuse and Mental Health Services Administration (SAMHSA). Medications for Opioid Use Disorder for Healthcare and Addiction Professionals, Policymakers, Patients, and Families TIP 63. Rockville, MD: U.S. Department of Health and Human Services, 2021. Available at https://www.ncbi.nlm.nih.gov/books/NBK574910/pdf/Bookshelf_NBK574910.pdf.

   b. Several scales can be used to monitor the severity of opioid withdrawal symptoms. One of the most commonly used is the Clinical Opiate Withdrawal Scale (COWS). It consists of 11 items that are scored from 0 (asymptomatic) to 4 or 5 (severely symptomatic). The maximum score is 48. A score of 5–12 is considered mild, whereas a score of greater than 36 is severe.
   c. First-line treatment for severe withdrawal is buprenorphine or methadone (see Methadone and Buprenorphine sections in the text that follows for details).
   d. Lofexidine (Lucemyra) is FDA approved for the treatment of opioid withdrawal. Although less effective than methadone or buprenorphine for withdrawal symptoms, it is appropriate for use when neither methadone nor buprenorphine is available for use. It is an α_2-adrenergic agonist that reduces the release of norepinephrine and reduces sympathetic tone. It has higher selectivity for the α_{2A}-receptor and is thus thought to be less antihypertensive than clonidine. Lofexidine is intended to treat symptoms of opioid withdrawal, and not for long-term therapy to reduce the risk of relapses. It can prolong the QTc interval and thus should be avoided or administered with caution in patients receiving methadone. Clonidine is used off-label because of the similar mechanism of action and cheaper price.

4. Medications for OUD: Pharmacologic therapies for maintenance treatment of OUD include methadone, naltrexone, and buprenorphine with or without naloxone.
   a. Medication is integral, but not mandatory, to recovery for many people with OUD. Medications used to treat OUD are superior to placebo or no medication for reducing illicit use, maintaining treatment retention, and reducing opioid overdose death. OUD medication allows time for the individual to make necessary life changes that correlate with long-term remission and recovery. Although it should be considered for all patients with OUD, the strongest consideration should be made for patients with moderate to severe OUD.
   b. Pharmacologic treatment of OUD should be integrated with outpatient and/or residential treatment and facilitated between transitions of care, whether inpatient to outpatient, or from emergency department visit to outpatient follow-up. Patients can benefit from psychotherapy and individualized social supports.

5. Methadone (Dolophine) (C-II)
    a. Has the most extensive evidence base supporting treatment of OUD. It is the most studied and most widely used medication for severe OUD. The World Health Organization considers it an essential medication.
    b. Full agonist with an affinity for the opioid mu-opioid receptor
    c. Boxed warnings
        i. Fatal respiratory depression: Methadone has a long half-life and is highly lipophilic and may be released slowly from tissue once it accumulates there. For this reason, respiratory depression can occur after the analgesic effects peak; thus, overdose is a risk, particularly during initiation, conversion from another opioid agonist, or a dose increase. There is also an increased risk of respiratory depression when combined with benzodiazepines or other CNS depressants.
        ii. Prolonged QTc interval and torsades de pointes can occur. The risk is dose related and more common with daily doses greater than 200 mg, though it has been reported with lower doses used to treat OUD. Appropriate monitoring is indicated. Screen for risk factors for a prolonged QTc, and avoid combining with other agents that can prolong the QTc interval. If the QTc exceeds 500 milliseconds, it is recommended to decrease or discontinue the methadone dose, eliminate other risk factors for QTc prolongation (if possible), and consider an alternative medication, such as buprenorphine.
    d. Metabolized by CYP3A4; dose should be adjusted for inducers and inhibitors
    e. Standard of care for pregnancy, though buprenorphine use is increasing. May be beneficial with fewer adverse effects
    f. According to the Code of Federal Regulations title 32, section 8: Methadone products for the treatment of OUD are only available through federally regulated opioid treatment programs. Methadone is administered as a single liquid daily dose in a supervised outpatient treatment setting. Patients must come to the opioid treatment program to receive their dose. Arrangements can be made for a single take-home dose on days the treatment clinic is closed. Exceptions can be made for inpatient or emergency treatment. These programs must offer other services, including medical, counseling, vocational, and educational.
    g. Urine drug tests do not routinely screen for methadone. Additional specialized testing is required.
6. Buprenorphine (Subutex, Bunavail, Suboxone, Zubsolv, Sublocade) (C-III; with or without naloxone)
    a. Use of buprenorphine came about as a result of the Drug Addiction Treatment Act of 2000 (DATA 2000), which allows qualifying physicians to apply for a waiver to treat opioid addiction outside an opioid treatment program using schedule III, IV, and V medications that are FDA approved for this indication. The Consolidated Appropriations Act of 2023 mandates 8 hours of buprenorphine-specific training for all providers before the next Drug Enforcement Administration renewal.
    b. Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist of the kappa receptor. The mu-opioid receptor binding affinity is higher than that of full-opioid agonists with a lower intrinsic activity. Thus, buprenorphine will displace morphine, methadone, and other opioid drugs but only gives a fraction of effect that levels out with increasing doses. This ceiling effect may not provide enough craving control if a patient used high doses of opioid. This allows patients enough effect to "feel normal" but minimizes functional impairment. This also makes the drug safer in overdose situations. At high-enough doses, the kappa antagonist properties can precipitate withdrawal.
    c. The partial mu-agonist activity makes buprenorphine less likely to cause respiratory depression. Lethal overdoses are possible, particularly in opioid-naive patients or individuals who combine it with other CNS depressants such as benzodiazepines or alcohol.
    d. Adding naloxone reduces abuse potential because naloxone is more rapidly inactivated after oral/sublingual absorption than after parenteral administration. Thus, if the medication is used as intended (sublingually), the likelihood of withdrawal symptoms is low as opposed to dissolving and injecting it.

e. Like with methadone, the World Health Organization considers buprenorphine an essential medication.
f. Dosage forms:
    i. Short-acting buprenorphine: Sublingual tablets (Subutex)
    ii. Short-acting buprenorphine/naloxone (4:1 dosing ratios): Buccal film (Bunavail), sublingual film (Suboxone), sublingual tablet (Zubsolv)
    iii. Long-acting buprenorphine formulations: ER injection (Sublocade)
g. Treatment with buprenorphine involves three phases: induction, stabilization, and maintenance. Buprenorphine/naloxone is preferred for most patients, including those taking short-acting opioids (hydromorphone, oxycodone, heroin). Patients taking long-acting opioids (methadone, long-acting morphine, long-acting oxycodone) should be tapered to methadone 30 mg/day or less (or the equivalent) and transitioned to buprenorphine first. It is recommended that these patients be changed to the buprenorphine/naloxone combination after no more than 2 days of buprenorphine monotherapy.
    i. They must also be screened for other SUDs and for appropriateness of buprenorphine therapy. Patients should begin buprenorphine when they have clear signs of opioid withdrawal. In these cases, the opioid receptors are not fully occupied, and buprenorphine is less likely to induce withdrawal. If the patient is transitioning from methadone, it may take 24–48 hours after the last methadone dose for opioid withdrawal symptoms to manifest.
    ii. Patients should receive concomitant counseling and nonpharmacologic treatment support during treatment. Counseling should consider all psychosocial factors.
    iii. Induction phase: Find the lowest buprenorphine dose that minimizes cravings for opioids but prevents withdrawal symptoms. Induction can occur in an inpatient setting, an outpatient office setting, or at home. Office induction is preferred for several reasons, including ensuring the patient knows how to take the medication, improving the therapeutic alliance, verifying the presence of opioid withdrawal symptoms and the absence of precipitated withdrawal symptoms, ensuring the lack of sedation 1–2 hours after taking the medication, and using the time between doses for patient self-monitoring. The patient is given a 2- to 4-mg dose of buprenorphine or the 2/0.5-4/1 mg dose of buprenorphine/naloxone. If withdrawal symptoms are not relieved or return before the 2-hour period, a repeat dose is given, up to a total dose of 8 mg or 8/2 mg on day 1. The dose established during the induction phase depends on the presence of withdrawal symptoms on subsequent days, to a maximum of 32/8 mg/day. Clinically significant differences are not usually seen with doses greater than 24 mg/day of buprenorphine.
    iv. Stabilization phase: Reached when the patient is without withdrawal symptoms, is not experiencing adverse effects of buprenorphine/naloxone, and no longer has uncontrollable symptoms of craving. Toxicology screens can be used to verify the patient is not using opioids. Patients should be seen weekly until stable. Doses can be adjusted in 2/0.5-mg to 4/1-mg increments. Most patients are maintained on 16/4 to 24/6 mg/day.
    v. Maintenance phase: Once the lowest dose needed to maintain abstinence is reached, buprenorphine/naloxone therapy can be maintained indefinitely. Nonpharmacologic modalities should continue during this time.
    vi. Discontinuation: This should be considered only if the patient is psychologically and medically stable, can maintain a drug-free lifestyle, and no longer feels the drug is necessary to remain abstinent. The medication should be tapered slowly to avoid withdrawal symptoms.
h. The ER subcutaneous buprenorphine injection can be used after induction and adjustment to 8–24 mg daily using a transmucosal formulation of buprenorphine. The dosing is 300 mg monthly for the first 2 months, followed by the usual maintenance dose of 100 mg monthly. If patients have suboptimal clinical response to the 100-mg dose, it can be increased to a maximum of 300 mg. The injected liquid forms a solid mass upon contact with body fluids. For this reason, it carries a boxed warning for

risk of serious harm (including occlusion, local tissue damage, and thromboembolic events, including pulmonary emboli) or death with intravenous administration. Health care facilities and pharmacies that order and dispense it must be certified through the Sublocade REMS program. As part of this program, the subcutaneous liquid product can only be dispensed to a health care provider for administration by a health care provider. It cannot be dispensed directly to a patient. Buprenorphine is metabolized by CYP3A4. Use caution with other medications that either induce or inhibit 3A4.

7. Naltrexone (ReVia, Vivitrol)
    a. Either the daily tablet or the ER injectable can be used, but the ER injectable is usually preferred because of better adherence.
    b. The ER injectable is part of a REMS education program. Patients must be counseled on the following points:
        i. Risk of increased opioid sensitivity and opioid overdose
        ii. Risk of severe reactions at the injection site
        iii. Risk of liver injury, including liver damage or hepatitis
        iv. Therapeutic effects of opioid medications taken for pain, cough and cold, or diarrhea may not be felt by the patient.
    c. Unlike methadone and buprenorphine, prescription and administration of naltrexone are not restricted by practice setting or prescriber.
    d. The patient must be completely off opioids for 7–10 days before naltrexone is administered (14 days if taking methadone or buprenorphine).
    e. If initiated before release from a controlled environment in which the patient has undergone opioid withdrawal, it can help prevent a return to opioid use. Because naltrexone does not provide opioid agonism, it may not be effective in patients experiencing severe cravings. This presents a risk because the patient may try to overcome the antagonism of naltrexone with high-dose opioids, which can lead to overdose and respiratory depression.

J. Nicotine Dependence
1. Nicotine use is the main cause of preventable morbidity and mortality in the United States.
2. Smoking cessation reduces the risk of several adverse health effects, including reproductive health outcomes, cardiovascular diseases, chronic obstructive pulmonary disease (COPD), and cancer. It is also beneficial to those with preexisting cardiovascular disease and COPD.
3. According to the CDC, 11.5% of adults smoked cigarettes in 2021. Rates of nicotine use have greatly declined over the past decade, and there are now more former smokers than current smokers.
4. Smoking cessation counseling is not consistently offered and tends to be directed to patients with tobacco-related conditions. Interventions lasting as few as 3 minutes can make a difference. Patient counseling can help encourage patients who are unwilling to quit to reconsider quitting and act on it in the future.
5. As of January 2015, the Joint Commission requires inpatient psychiatric services to screen for tobacco use (TOB-1), offer or provide treatment for tobacco dependence (TOB-2), and provide or offer treatment for tobacco dependence at discharge (TOB-3).
6. On average, seven attempts are necessary for a patient to quit successfully.
7. Willingness to quit should be assessed by the five A's: *ask* about tobacco use, *advise* to quit, *assess* willingness to attempt to quit, *assist* in quit attempt, and *arrange* for follow-up.
8. Motivational interviewing can help identify barriers to change and help the patient overcome them.
9. The five R's can increase motivation to quit: relevance, risks, rewards, roadblocks, and repetition.
10. Quit lines such as 1-800-QUIT-NOW can facilitate attempts.
11. Seven pharmacologic agents (five nicotine and two non-nicotine) are available to help. They should be used with nonpharmacologic modalities to increase the success of quitting.

12. A usual pack contains 20 cigarettes.
13. Nicotine replacement therapy: All forms are equally efficacious. Patients should be advised to stop smoking completely before initiating. Nicotine replacement therapy is available in the following forms:
    a. Patch: For patients who smoke more than 10 cigarettes/day, start with 21 mg/day for 6 weeks (4 weeks if Habitrol), then 14 mg/day for 2 weeks, then 7 mg/day for 2 weeks. For those who smoke 10 cigarettes/day or less, start with 14 mg/day for 6 weeks, then 7 mg/day for 2 weeks. Patches may be used for longer periods, if needed, to improve success. The patch should be changed when awakening every day. If the patch causes sleep disturbances, including disturbing or vivid dreams, it can be removed at bedtime. Rotate sites.
    b. Gum: The gum should be chewed until a "peppery" or flavored taste develops; it should then be "parked" between the cheek and gum to facilitate buccal absorption. The gum should be chewed and parked for 30 minutes or until the flavor is gone. No food or drink (other than water) should be taken during or for 15 minutes before or after using the gum. The maximum amount of gum to use is 24 pieces in 24 hours. At least 9 pieces of gum should be used daily to increase the chances of quitting. Patients who smoke their first cigarette within 30 minutes of waking should use the 4-mg strength. Otherwise, the 2-mg dose is used. One piece of gum should be used every 1–2 hours for the first 6 weeks of therapy, followed by 1 piece every 2–4 hours for weeks 7–9, then 1 piece every 4–6 hours for weeks 10–12. Acidic beverages (e.g., coffee, juices, and soft drinks) interfere with buccal absorption and should be avoided at least 15 minutes before using the gum. Adverse effects include soreness, dyspepsia, hiccups, and jaw ache. These are usually mild and can be corrected with changes in chewing technique.
    c. Lozenge: Patients who smoke their first cigarette within 30 minutes of waking should use the 4-mg strength. Otherwise, the 2-mg dose is used. The lozenge should be dissolved in the mouth rather than chewed or swallowed. No food or drink should be taken during or for 15 minutes before or after using the lozenge. The frequency of use and tapering are the same as for the gum. Adverse effects are also similar. At least 9 lozenges should be used at the beginning to increase chances of quitting. Only 1 lozenge should be used at one time. No more than 5 lozenges within 6 hours, maximum 20 lozenges/24 hours
    d. Inhaler: Available by prescription only in the United States. Each cartridge delivers 4 mg of nicotine over 80 inhalations. The recommended dosing is 6–16 cartridges/day. Results are best if the contents of the cartridges are continuously puffed over about 20 minutes. Recommended treatment length is 3 months, with reduction in frequency during the last 6–12 weeks. As with the gum and lozenges, patients should not drink acidic beverages or eat within 15 minutes of using the inhaler. Delivery decreases at less than 40°F, so the inhaler should be kept in an inner pocket in cold weather. The most common adverse effects are sore throat, coughing, and rhinitis. Inhalers should be avoided in patients with reactive airway diseases.
    e. Nasal spray: Available by prescription only. The dose is 0.5 mg delivered to each nostril. One or two doses should be used hourly, up to five doses. The 24-hour maximum is 40 doses. At least eight doses should be used at the start of therapy. Each bottle contains 100 doses. Recommended length of therapy is 3–6 months, with tapering. Risk of dependency is higher than with other forms of nicotine replacement. Inhaling, sniffing, and swallowing can increase the risk of nasal irritation and should thus be avoided when using the spray. Nasal irritation can occur in up to 94% of patients. Although nasal irritation can resolve, many patients may have it as long as 8 weeks into therapy. Nasal spray is not recommended for patients with reactive airway diseases or nasal conditions.
    f. Nicotine patches can be used with the as-needed dosage forms to increase the chances of quitting.
    g. Patients with a history of cardiovascular disease can use nicotine replacement therapies.

h. The treatment of choice in pregnant women is nonpharmacologic. Nicotine is freely transferred to the fetus throughout pregnancy. Use of cigarettes or nicotine gum in the third trimester has been associated with diminished breathing movement in the fetus. The FDA has developed labeling for nicotine replacement products in pregnancy. Although the FDA advises using these products only on the advice of a health care provider, it also states that the products are believed to be safer than smoking.

14. Bupropion SR: Should be initiated 7 days before the quit date. Treatment should last for at least 8 weeks but can be continued for up to 6 months to increase the chances of quitting. Bupropion can also be combined with the nicotine patch, if needed.
15. Varenicline: A nicotine receptor partial agonist. Varenicline blocks the effects of nicotine from smoking. Varenicline should be started 1 week before the quit day, though patients can choose to quit smoking up to 35 days after starting varenicline. Varenicline should be continued for a total of 12 weeks. If the patient is successful at smoking cessation, varenicline can be continued for another 12 weeks. The boxed warning about neuropsychiatric symptoms was removed in 2016. A meta-analysis and systematic review showed that the risk of neuropsychiatric symptoms was not significantly different from placebo (BMJ 2015;350:h1109). An FDA advisory warned of a small increase in the risk of cardiovascular events, particularly in patients with preexisting cardiovascular disease. The benefits of smoking cessation must be weighed against the possible risk. Varenicline must be used with caution in patients with a CrCl less than 30 mL/minute/1.73 m^2. Combining varenicline with nicotine replacement therapy may increase adverse effects, though varenicline has been used in combination with the nicotine patch. Varenicline can be combined with bupropion.
16. Other agents used include clonidine and nortriptyline.
17. Patients who were unsuccessful in quitting on one form of pharmacologic therapy should be tried on a different method.
18. The American Thoracic Society has released guidelines for initiating pharmacologic treatment in tobacco-dependent adults. The ATS makes five strong recommendations and two conditional recommendations.
    a. Strong recommendations: For tobacco-dependent adults in whom treatment is being initiated:
        - Varenicline is recommended over a nicotine patch.
        - Varenicline is recommended over bupropion.
        - Varenicline plus a nicotine patch is recommended over varenicline alone.
        - Varenicline is recommended over electronic cigarettes.
        - In patients who are not ready to discontinue tobacco use, it is recommended to start varenicline treatment rather than wait until patients are ready to stop.
    b. Conditional recommendations:
        - For tobacco-dependent adults with comorbid psychiatric conditions in whom treatment is being initiated, varenicline is recommended over a nicotine patch.
        - For tobacco-dependent adults, extended-duration (more than 12 weeks) therapy with varenicline is recommended over standard-duration (6–12 weeks) therapy.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: A

This patient is experiencing antipsychotic-induced acute dystonias. Benztropine or another anticholinergic should be given to reverse the EPS (neck stiffness and oculogyric crisis) (Answer A is correct). Dantrolene is used for patients with NMS but does not reverse acute dystonias (Answer B is incorrect). Propranolol is useful for akathisia but not for other types of EPS (Answer D is incorrect). Lorazepam can also be used for acute dystonias, but anticholinergic agents are usually preferred. In addition, this patient has a dual diagnosis of SUD; thus, benzodiazepines should be avoided unless absolutely needed (Answer C is incorrect).

2. Answer: B

Aripiprazole has less risk of EPS than haloperidol/FGAs but still carries a risk of EPS (Answer A is incorrect). Although SGAs such as aripiprazole may help reduce negative symptoms, they rarely eliminate them (Answer C is incorrect). Aripiprazole has no evidence to support its use to treat SUDs (Answer D is incorrect). The best reason to use aripiprazole in this patient is that aripiprazole can be converted to an LAI formulation that can be given monthly (Abilify Maintena) or up to every 8 weeks (Aristada) (Answer B is correct).

3. Answer: C

Among the SGAs, aripiprazole is more likely to cause akathisia, which is a form of EPS that involves a subjective feeling of restlessness and inability to sit still (Answer C is correct). Aripiprazole has a low incidence of sedation (Answer A is incorrect). Anticholinergic effects are minimal with aripiprazole (Answer B is incorrect). Although all antipsychotics can potentially cause QTc prolongation, they rarely cause problems in patients without risk factors (Answer D is incorrect).

4. Answer: D

Ziprasidone would be most appropriate, given the patient's history of dystonia with haloperidol (Answer D is correct). Ziprasidone carries a lower risk of causing EPS than FGAs such as fluphenazine (Answer B is incorrect). Clozapine and olanzapine have low risks of EPS as well, but clozapine is reserved for treatment-resistant cases (Answer A is incorrect). Olanzapine would not be preferred because of the significant metabolic risks it could cause in this young patient. Most of the current guidelines for schizophrenia do not consider olanzapine a first-line agent for a patient with newly diagnosed schizophrenia (Answer C is incorrect).

5. Answer: C

Paroxetine would have the most interaction with this patient's current medications because of its interaction with hydrocodone by inhibiting the 2D6 isoenzyme (Answer C is correct). This would result in a lack of analgesic effects from the opiate. Fluvoxamine is a 1A2 inhibitor that does not interact with thiazides, metformin, or opiates (Answer B is incorrect). Citalopram would have no appreciable effects on any of this patient's medications (Answer A is incorrect). The effect of sertraline, though it may compete with hydromorphone (metabolite of hydrocodone) through 3A4, would be less than that of paroxetine (Answer D is incorrect).

6. Answer: C

Mirtazapine is appropriate because it can improve this patient's insomnia and poor appetite (Answer C is correct). In addition, mirtazapine has no drug-drug interactions with the patient's current medications. Bupropion, fluoxetine, and venlafaxine would worsen the patient's insomnia (Answers A, B, and D are incorrect). Although venlafaxine might help the pain, it could worsen hypertension at doses greater than 150 mg daily (Answer D is incorrect), and bupropion decreases appetite, is a strong inhibitor of 2D6, and is contraindicated in eating disorders (Answer A is incorrect).

7. Answer: B

The citalopram dose should be increased to 40 mg/day because this patient had some initial response to the drug (improvement in insomnia and appetite) but may not have reached the maximum tolerated dose (Answer B is correct). The patient has taken citalopram for only 4 weeks, possibly at a subtherapeutic dose (Answer A is incorrect). Adjunctive therapy with SGAs such as aripiprazole should be reserved for patients who have had partial response to therapeutic doses of antidepressants (e.g., citalopram 40 mg daily for at least 4 weeks) (Answer C is incorrect). Changing SSRIs may also be an option after the maximum tolerated citalopram dose is reached (Answer D is incorrect).

8. Answer: D
The patient still needs an antidepressant, and discontinuing citalopram without an alternative agent at 6 months would be inappropriate (Answer A is incorrect). Bupropion is sometimes added to antidepressants for treatment-emergent sexual dysfunction, with some evidence of efficacy. However, bupropion should be avoided in patients with a history of eating disorders, including bulimia (Answer B is incorrect). Changing to a different SSRI might produce the same adverse effect because the patient's anorgasmia appears to be caused by serotonergic activity (Answer C is incorrect). Vortioxetine is associated with a lower incidence of sexual dysfunction than SSRIs. Trial data analyses show that patients with sexual dysfunction taking SSRIs, including citalopram, can have an improvement in their sexual dysfunction when changed to vortioxetine (Answer D is correct).

9. Answer: D
Lithium should be initiated to treat the current manic phase and prevent future episodes (Answer D is correct). Carbamazepine is effective for maintenance treatment but is considered second or third line for acute mania (Answer A is incorrect). Divalproex is also good for maintenance treatment, but given this patient's active hepatitis C, it would not be a good choice (Answer B is incorrect). Lamotrigine is also effective for maintenance but not for treating the patient's current manic phase (Answer C is incorrect).

10. Answer: B
Coarse tremor may indicate lithium toxicity and will require an immediate evaluation of the patient's lithium concentration (Answer B is correct). Lithium can cause hypothyroidism, severe acne, and weight gain, but these can usually be managed with lifestyle modifications or medications (Answers A, C, and D are incorrect).

11. Answer: C
This patient has lithium toxicity, as evidenced by the lithium concentration (1.9 mEq/L) and the accompanying symptoms of confusion and slurred words. Ibuprofen can increase lithium concentrations. It was started in the past week and is thus the most likely culprit (Answer C is correct). Zolpidem might increase sedation, but it should not result in the current symptoms (Answer D is incorrect). The sodium in the oral rehydration solution would be expected to decrease, not increase, the lithium concentrations (Answer B is incorrect). Amlodipine does not affect lithium concentrations (Answer A is incorrect).

12. Answer: C
This patient is experiencing a depressive phase of bipolar disorder. Divalproex sodium is more efficacious for manic or mixed episodes and should also be avoided in women of childbearing age, if possible (Answer A is incorrect). Lamotrigine is used for the depressive phase, but it must be titrated slowly to avoid rash. Thus, lamotrigine is not the best choice for an acute episode (Answer B is incorrect). An SNRI such as venlafaxine might increase the risk of switching to mania (Answer D is incorrect). Quetiapine is used for depression associated with bipolar disorder and might also help her sleep at night and improve her appetite (Answer C is correct).

13. Answer: A
Paroxetine should be continued at this time because the patient is successfully being treated for depression, and paroxetine is considered first line for PTSD (Answer A is correct). Sertraline also treats PTSD, but there is no reason to discontinue paroxetine (Answer B is incorrect). Adding adjunctive agents such as lorazepam and buspirone is not indicated because paroxetine was initiated only 3 weeks ago (Answers C and D are incorrect).

14. Answer: C
Both SSRIs and SNRIs are considered first line for GAD and are associated with symptom remission (Answer C is correct). Although benzodiazepines such as alprazolam can relieve symptoms, they are only recommended for short-term treatment (Answer A is incorrect). Although buspirone is effective for GAD, it is not considered first line (Answer B is incorrect). Pregabalin is effective for GAD, but its use is off-label, and it is usually reserved for patients who do not respond to, or cannot tolerate, antidepressants (Answer D is incorrect).

15. Answer: A
Although antidepressants such as paroxetine and venlafaxine are the cornerstones for treating panic disorder, they take time to work and can worsen symptoms when first initiated (Answers C and D are incorrect). Benzodiazepines effectively treat the acute symptoms of panic disorder and are indicated when panic attacks

significantly affect a patient's ability to function in everyday life, such as attending a job (Answer A is correct). Ideally, an antidepressant should be initiated with the benzodiazepine, and the benzodiazepine should later be withdrawn once the patient's condition is stable on the antidepressant. Buspirone is not effective for panic disorder (Answer B is incorrect).

16. Answer: C
Serotonergic activity is necessary for efficacy against OCD. First-line agents include selected SSRIs (escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) and clomipramine (Answer C is correct). Desipramine is a secondary amine TCA and has no significant serotonergic activity (Answer B is incorrect). Bupropion has no serotonergic activity (Answer A is incorrect). Mirtazapine does not currently have strong evidence for efficacy in the treatment of OCD (Answer D is incorrect). For these reasons, only fluoxetine would be a viable option for treatment.

17. Answer: D
The patient takes levothyroxine at night, which is probably contributing to insomnia (Answer D is correct). Hydrochlorothiazide and ibuprofen are not significantly associated with causing insomnia (Answers B and C are incorrect). Citalopram may contribute to insomnia in certain patients, but this patient takes it in the morning, which decreases the risk (Answer A is incorrect).

18. Answer: D
The patient does not want a drug with significant daytime sedation but needs a drug that will help sustain sleep throughout the night. Zolpidem is the best option (Answer D is correct). Trazodone has a long half-life that will help the patient stay asleep but has fewer efficacy data for insomnia (Answer A is incorrect). Temazepam causes daytime sedation (Answer B is incorrect). Zaleplon does not cause daytime sedation, but its short half-life would not help the patient stay asleep (Answer C is incorrect).

19. Answer: C
Zolpidem and other sedative-hypnotics have been associated with abnormal behaviors such as eating, driving, having sex, and talking on the telephone while asleep (Answer C is correct). Zolpidem may cause orthostasis and disorientation but, when taken appropriately, does not cause significant problems (Answers A and B are incorrect). Zolpidem at high doses has been associated with seizures, but this patient has no history of drug abuse or of using high doses of medications (Answer D is incorrect).

20. Answer: C
The initial symptoms of alcohol withdrawal include hemodynamic instability such as increased heart rate and blood pressure (Answer C is correct). Alcohol craving, delirium tremens, and seizures generally occur after 12 hours of abstinence (Answers A, B, and D, respectively, are incorrect).

21. Answer: D
Lorazepam is appropriate because of the patient's liver abnormalities (Answer D is correct). Lorazepam undergoes glucuronidation and does not rely on oxidative pathways for metabolism. Chlordiazepoxide and diazepam should be avoided in patients with liver disease because of the presence of active metabolites with long half-lives (Answers A and C are incorrect). Clonazepam is generally not used for alcohol withdrawal (Answer B is incorrect).

22. Answer: A
Given the patient's liver disease, acamprosate is most appropriate because it does not rely on hepatic metabolism (Answer A is correct). Disulfiram is not generally recommended in patients with liver disease (Answer C is incorrect). Naltrexone is not indicated in patients with liver function tests greater than 3 times the upper limit of normal (Answer D is incorrect). Diazepam is not used for alcohol dependence but is used during alcohol withdrawal (Answer B is incorrect).

23. Answer: D
For opioid detoxification in the outpatient setting, the combination buprenorphine/naloxone product is preferred (Answers A and B are incorrect). The correct initial dose is 4/1 (Answer D is correct; Answer C is incorrect).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: D

The patient's symptoms most closely resemble akathisia. The treatment of choice in this case is a lipophilic β-blocker such as propranolol (Answer D is correct). Benztropine is an anticholinergic agent that can be used for other movement disorders such as dystonias or parkinsonian symptoms, but it is not effective for akathisia (Answer A is incorrect). Benzodiazepines are effective for akathisia, but they are not the best choice, given this patient's history of alcohol use disorder (Answer C is incorrect). Dantrolene, a skeletal muscle relaxant, is used for NMS (Answer B is incorrect).

2. Answer: D

This patient has tardive dyskinesia, which involves abnormal, repetitive, involuntary movements. Involvement of the facial muscles, including the jaw, is common. Until recently, very little treatment was available for tardive dyskinesia. In patients with new-onset, mild tardive dyskinesia, discontinuing the suspected antipsychotic or changing to an agent with less likelihood of causing tardive dyskinesia was an option. Of the antipsychotics, clozapine is considered least likely to cause tardive dyskinesia and is thus an agent of choice in patients who develop tardive dyskinesia. Clozapine is also the agent of choice in patients who do not respond to at least two trials of other antipsychotics, including both FGAs and SGAs. This patient's condition is stable on the current regimen (perphenazine), but the patient has not responded to or has not tolerated several other antipsychotics. The patient also developed diabetes while taking olanzapine, which is closely related to clozapine. For this reason, changing to clozapine would not be best (Answer C is incorrect). Treatments for other forms of EPS, including benztropine and lorazepam, are ineffective for tardive dyskinesias (Answers A and B are incorrect). On April 11, 2017, the FDA approved valbenazine for the treatment of tardive dyskinesia. In a systematic review of its effects, valbenazine had a number needed to treat of 4 to reduce the Abnormal Involuntary Movement Scale by 50% or more, with a number needed to harm (somnolence) of 15. In this patient, who is responding well to the current antipsychotic treatment, valbenazine would be the best choice (Answer D is correct).

3. Answer: B

Clozapine is metabolized by CYP1A2, an enzyme that is induced by smoking. Smoking cessation can reverse this induction and cause supratherapeutic concentrations of clozapine, resulting in dose-dependent seizures (Answer B is correct). Although bupropion can also cause seizures, the patient has been stable on this dose for 1 month (Answer A is incorrect). Neither diphenhydramine nor metformin is associated with drug-induced seizures at the current doses (Answers C and D are incorrect).

4. Answer: B

Of the agents listed, mirtazapine and the SSRIs fluoxetine and paroxetine are considered first line. Fluoxetine's adverse effect profile most closely counteracts the patient's symptoms. Fluoxetine is activating and can improve this patient's ability to get out of bed. This patient also has anxiety, and fluoxetine could concomitantly relieve the symptoms of anxiety and allow for discontinuation of the benzodiazepine (Answer B is correct). Paroxetine can increase appetite and cause somnolence (Answer D is incorrect), as can mirtazapine (Answer C is incorrect). Although the suicidal ideation is intermittent and passive, desipramine can be fatal in an overdose situation (Answer A is incorrect).

5. Answer: B

Duloxetine is the best choice because it is also indicated for diabetic neuropathy (Answer B is correct). Although nortriptyline is effective for neuropathy, it is not a good choice in a patient with cardiovascular disease. Nortriptyline can also cause weight gain (Answer C is incorrect). Although bupropion is either weight neutral or can lead to some weight loss, data are not strong for its use in neuropathy (Answer A is incorrect). Sertraline would be safe in this patient and could be used as an alternative to citalopram, but it is not effective for neuropathy (Answer D is incorrect).

6. Answer: D

This patient has serotonin syndrome (myoclonus, agitation, diaphoresis). The symptoms are probably caused by adding dextromethorphan to paroxetine. In addition to the serotonergic activity of both agents, paroxetine inhibits CYP2D6, which is responsible for metabolizing dextromethorphan. This further increases the serotonergic activity (Answer D is correct). None of the

other choices is a combination of serotonergic agents, nor do they interact in a fashion that would increase serotonergic activity (Answers A–C are incorrect).

7. Answer: C

This patient is having an acute depressive episode. The patient has taken lithium for 5 years, which is long enough to derive any antidepressant effects. The lithium concentration is also within therapeutic range. Quetiapine is FDA indicated for depression associated with bipolar disorder (Answer C is correct). Lithium's onset of action is more rapid than that of lamotrigine, which requires a slow titration to reach therapeutic doses (Answer B is incorrect). Unlike data for aripiprazole in unipolar depression, data analyses for aripiprazole suggest it is not effective for bipolar depression (Answer A is incorrect). The efficacy of antidepressants in treating type I bipolar disorder is questionable, and treatment with an SNRI could lead to a switch to mania (Answer D is incorrect).

8. Answer: D

This patient has hypothyroidism, as indicated by the increased thyrotropin concentrations. The hypothyroidism was probably induced by lithium (Answer D is correct). The glucose is likely elevated secondary to lithium-induced hypothyroidism and is not directly related to lithium therapy (Answer A is incorrect). Even though lithium can "look like" sodium to the body, lithium does not commonly affect sodium concentrations. This patient's sodium concentrations are within the normal range (Answer C is incorrect). Although lithium can impair renal function, this patient's serum creatinine concentration is within the normal range (Answer B is incorrect).

9. Answer: B

This patient's presentation and laboratory results are consistent with acute pancreatitis. Although the incidence of pancreatitis is rare, divalproex can cause this condition. Patients who develop pancreatitis while taking divalproex that resolves when the patient is no longer taking the agent should not be rechallenged (Answer B is correct). Neither aripiprazole nor lamotrigine is associated with pancreatitis (Answers A and C are incorrect). This patient's lamotrigine dose should be lowered to prevent Stevens-Johnson syndrome. Despite lamotrigine's temporal relationship with prednisone, it is probably not contributing to the current clinical picture (Answer D is incorrect).

10. Answer: D

This patient has panic disorder. Benzodiazepines more rapidly treat the acute physical symptoms and fear that occur with panic disorder, but they are not the agents of choice for long-term symptom control (Answer A is incorrect). Selective serotonin reuptake inhibitors such as paroxetine are first line for preventing panic attacks. Although they take time to achieve full efficacy, they are the most effective for maintenance control of symptoms (Answer D is correct). Buspirone is not effective acutely for panic attacks (Answer B is incorrect). Hydroxyzine might offer some sedation, but it would not treat the underlying anxiety disorder (Answer C is incorrect).

11. Answer: C

Although SSRIs and SNRIs are the first-line treatment for GAD, the patient has not responded to several antidepressants. Although it does not carry an FDA indication, pregabalin is also effective against GAD. Several guidelines list it as first- or second-line agent. Pregabalin is similar to antidepressants and benzodiazepines, so it might be a good choice in this patient (Answer C is correct). Venlafaxine has proven efficacy for GAD, but given this patient's lack of response to other antidepressants, it might be suboptimal compared with pregabalin (Answer D is incorrect). Fluoxetine is effective for GAD but is a strong inhibitor of CYP2D6, which would decrease the efficacy of tamoxifen (Answer B is incorrect). Bupropion is also an inhibitor of CYP2D6 and is ineffective against most anxiety disorders (Answer A is incorrect).

12. Answer: B

This patient primarily has difficulty with sleep onset and would benefit from an agent that decreases sleep latency and does not prolong sleep. Ramelteon is the only listed agent that produces these effects. Older adults can have difficulty with circadian rhythm, which a melatonin analog may help regulate. Ramelteon is also indicated for chronic insomnia if needed for a prolonged period (Answer B is correct). Although eszopiclone decreases time to sleep, its longer half-life may result in hangover effects (Answer A is incorrect). Suvorexant also treats sleep maintenance, but it can also cause a hangover effect (Answer C is incorrect). Zolpidem received recent labeling changes for reduced doses and has reduced metabolism in older adults (Answer D is incorrect).

13. Answer: D

To avoid withdrawal symptoms, patients taking long-acting opioids should have doses tapered to the equivalent of methadone 30 mg/day or less before being changed to a buprenorphine regimen (Answer D is correct). Initiating a patient on buprenorphine at higher methadone doses could precipitate withdrawal because of the higher binding affinity of buprenorphine for the mu-opioid receptor with less activity and the added antagonism at the kappa receptor (Answer B is incorrect). Patients taking long-acting opioids such as methadone should be changed to buprenorphine monotherapy before being advanced to buprenorphine/naloxone (Answer A is incorrect). Naltrexone monotherapy is inappropriate because it can precipitate withdrawal (Answer C is incorrect).

14. Answer: A

This patient has alcoholic hepatitis, as indicated by the AST and ALT values. Presumably, these would improve with abstinence. Liver function is intact, as evidenced by albumin, prothrombin time, and platelet values. Naltrexone might be indicated in this patient, but opioids (methadone) are concomitantly present. Use of naltrexone in patients on methadone maintenance would precipitate withdrawal (Answer D is incorrect), though it could be considered once liver function tests correct. Disulfiram should be used with caution in patients with active liver disease. Disulfiram also requires a strong commitment on the patient's part to abstain from drinking and may be less effective. This patient has a history of several failed attempts (Answer C is incorrect). Chlordiazepoxide is used during acute alcohol detoxification but plays no role in maintenance therapy (Answer B is incorrect). The acamprosate dose should be reduced to 333 mg orally three times daily for a CrCl of 30–50 mL/minute/1.73 m^2 and is thus the most appropriate choice in this patient (Answer A is correct).

15. Answer: A

This patient's previous quit attempt with nicotine gum was probably unsuccessful because the gum strength (2 mg) and frequency of use (fewer than 9 pieces/day) were too low to manage the nicotine cravings. Thus, the previous use of nicotine gum is not a true treatment failure. The two cardinal symptoms suggestive of depression (sad affect and anhedonia) are present, making bupropion a reasonable choice (Answer A is correct). The myocardial infarction is not a contraindication to the use of nicotine products; thus, nicotine gum could be added to bupropion if monotherapy fails (Answers B and C are incorrect). Coronary artery disease is not a contraindication to varenicline therapy, but given this patient's likely concomitant depression, bupropion is a better fit (Answer D is incorrect).

Neurology

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Neurology

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Learning Objectives

1. Determine seizure type and appropriate use of antiepileptic drugs on the basis of their activity, adverse effects, and drug interactions for epilepsy and status epilepticus.
2. Establish appropriate interventions for primary and secondary prevention of stroke and appropriate treatment for acute stroke.
3. Assess pharmacotherapy for Parkinson disease.
4. Differentiate between regimens for acute and prophylactic treatment of migraine, tension, and cluster headaches.
5. Identify appropriate therapies for individuals with multiple sclerosis.
6. Establish appropriate treatment for peripheral neuropathy.

Abbreviations in This Chapter

ASM	Antiseizure medication
DAPT	Dual antiplatelet therapy
GABA	γ-Aminobutyric acid
MAO-B	Monoamine oxidase type B
MS	Multiple sclerosis
TIA	Transient ischemic attack

Self-Assessment Questions

Answers and explanations to these questions can be found at the end of this chapter.

1. E.S. is a 25-year-old electrician. He has had several episodes of memory lapses. His wife reports lip smacking and chewing movements during these spells. An electroencephalogram (EEG) reveals focal epileptiform spike waves. Which medication would be best for E.S.?
   A. Ethosuximide.
   B. Levetiracetam.
   C. Phenobarbital.
   D. Clobazam.

2. B.V. is a 48-year-old woman brought to your ED for the treatment of status epilepticus. Her blood glucose is 50 mg/dL on fingerstick. Which medication would be the best next treatment for B.V.?
   A. Lorazepam.
   B. Dextrose.
   C. Thiamine.
   D. Diazepam.

3. J.H. is a 42-year-old man with focal-onset seizures with loss of awareness for which he was prescribed levetiracetam. He comes to the clinic with concerns of agitation. He says his wife is also concerned because he is very irritable and, at times, depressed. Which best assesses J.H.'s condition?
   A. Discontinue levetiracetam; he is having adverse effects.
   B. Increase the levetiracetam dose; he is having focal seizures.
   C. Continue levetiracetam; it is controlling his seizures.
   D. Obtain a levetiracetam serum concentration; he is probably supratherapeutic.

Questions 4 and 5 pertain to the following case.

T.O. is a 68-year-old man who suddenly lost consciousness at home. His partner calls 911, and emergency medical technicians arrive within 10 minutes. According to the medical record, he experienced slurred speech and right arm weakness about 30 minutes before losing consciousness. He is treated for hypertension.

4. Which test would be best before initiating pharmacotherapy for T.O.?
   A. Cerebral angiogram.
   B. CT scan of head.
   C. Coagulation panel.
   D. Echocardiogram.

5. T.O. is diagnosed with a major ischemic stroke and treated with alteplase. He regains consciousness and is transferred to rehabilitation. Which treatment would be best for 3 months to prevent another stroke?
   A. Aspirin and clopidogrel.
   B. Aspirin and dipyridamole.
   C. Apixaban.
   D. Warfarin.

Questions 6 and 7 pertain to the following case.
P.P. is a 75-year-old woman who was diagnosed with Parkinson disease 8 years ago. During this visit to the clinic, she notes that her movements are slower and she feels stiffer. She has also experienced a worsening gait with two or three falls in the past 6 months. Her writing has also become small and illegible. She takes carbidopa/levodopa 25/100 mg 2 tablets four times daily.

6. Which of P.P.'s symptoms would best be controlled by pharmacotherapy?
   A. Gait disturbances.
   B. Falls.
   C. Handwriting.
   D. Rigidity.

7. P.P. notes that her symptoms seem worse before her next dose of carbidopa/levodopa. Which agent would best be added at this visit?
   A. Istradefylline.
   B. Entacapone.
   C. Apomorphine.
   D. Quetiapine.

8. W.S. is a 70-year-old man with newly diagnosed Parkinson disease who is initiated on carbidopa/levodopa. His symptoms are well controlled, but he has concerns of nausea and vomiting. Which intervention would be best to reduce his nausea and vomiting?
   A. Initiate promethazine.
   B. Initiate metoclopramide.
   C. Decrease carbidopa/levodopa.
   D. Initiate trimethobenzamide.

Questions 9 and 10 pertain to the following case.
R.M. is a 42-year-old man with headaches, which he describes as a tight band around his head. The headaches occur three or four times a week.

9. Which medication would be the best acute treatment for R.M. to use for his headaches?
   A. Naproxen.
   B. Sumatriptan.
   C. Dihydroergotamine.
   D. Lithium.

10. R.M is requesting a preventive medication to help reduce his headache frequency. Which agent would be best to recommend?
   A. Amitriptyline.
   B. Valproate.
   C. Topiramate.
   D. Frovatriptan.

Questions 11–13 pertain to the following case.
L.M. is a 43-year-old man diagnosed with relapsing-remitting multiple sclerosis (MS) 2 years ago. He has taken glatiramer acetate since then. However, his exacerbations have not discernibly decreased. He has spasticity in his legs, which has caused several falls in the past month, and fatigue that worsens as the day progresses.

11. Which medication would be best for L.M.'s MS?
   A. Cyclophosphamide.
   B. Methylprednisolone.
   C. Azathioprine.
   D. Fingolimod.

12. Which medication would be best for L.M.'s spasticity?
   A. Diazepam.
   B. Baclofen.
   C. Carisoprodol.
   D. Metaxalone.

13. Which medication would be best for L.M.'s fatigue?
    A. Propranolol.
    B. Lamotrigine.
    C. Amantadine.
    D. Ropinirole.

Questions 14 and 15 pertain to the following case.
B.T. is a 62-year-old man with obesity (weight 122 kg) who comes to the clinic with concerns of burning in the soles of his feet. These symptoms began about 3 months ago. They are worse at night and keep him from sleeping. On examination, he has decreased sensation in both feet up to the ankles bilaterally and good strength throughout his feet and legs. His ankle reflexes are decreased. He has hypertension treated with lisinopril 10 mg/day.

14. Which most likely caused B.T.'s pain and decreased sensation?
    A. Diabetic neuropathy.
    B. Chronic inflammatory demyelinating polyneuropathy.
    C. Entrapped nerve.
    D. Genetic neuropathy.

15. Which treatment would be best for B.T.'s symptoms?
    A. Carbamazepine 600 mg at bedtime.
    B. Lidocaine 5% patch applied to soles of feet at bedtime and removed in the morning.
    C. Acetaminophen 325 mg every 4 hours as needed.
    D. Valproate 250 mg twice daily.

BPS Pharmacotherapy Specialty Examination Content Outline

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline, tested during the Spring 2024 window:

1. Patient-Centered Pharmacotherapy
    a. 1.1: Develop patient-centered, evidence-based pharmacotherapy plans. Subtasks: 1.1.1 – 1.1.6, 1.1.8, 1.1.10 – 1.1.17.
    b. 1.2. Monitor the patient to ensure safe and effective pharmacotherapy. Subtasks: 1.2.1 – 1.2.4
    c. 1.3. Modify pharmacotherapy plans through ongoing patient assessment. Subtasks: 1.3.1 – 1.3.5.
    d. 1.5. Educate patients and caregivers on the safe and appropriate use of pharmacotherapy. Subtasks: 1.5.2, 1.5.3.

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline, tested starting Fall 2024:

1. Patient Care Specialty Areas
    a. 1A. Primary Pharmacotherapy Specialty Areas. Subtask: 1A4.
    b. 1B. Secondary Pharmacotherapy Specialty Areas. Subtask: 1B4.
2. Therapeutics and Patient Management
    a. 2A. Treatment Planning. Subtasks: 2A1 – 2A6.
    b. 2B. Therapeutic Implementation. Subtasks: 2B1, 2B2, 2B6.
    c. 2C. Treatment Outcomes and Monitoring. Subtasks: 2C1 – 2C5.
3. Professional Practice
    a. 3A. Quality of Care. Subtasks: 3A1 – 3A4.
    b. 3C. Practice Management. Subtask: 3C1.

I. EPILEPSY

A. Epidemiology
   1. Epilepsy is the fourth most common neurologic disorder. Ten percent of the U.S. population will have a seizure. Around 7.6 of 1000 individuals will develop epilepsy at some point in their lives (WHO 2019).
   2. Around 50 million people worldwide have epilepsy.
   3. Around 50% of newly diagnosed patients become seizure free on their first treatment, with up to 70% becoming seizure free after treatment adjustment and 30% continuing to have seizures (Neurology 2012;78:1548-54).

B. Classification of Seizures: Seizures are traditionally classified according to the International League Against Epilepsy (ILAE) scheme, adopted in 1981, with modifications in 2001 and 2010. In 2017 the ILAE developed and implemented a revised classification scheme for seizures..
   1. Focal-onset seizures start in an area or network of cells on one side of the brain.
      a. Focal seizures can further be classified as:
         i. Aware or impaired awareness
         ii. Motor or nonmotor
         iii. Focal or bilateral tonic-clonic
      b. The terms *simple partial seizure*, *complex partial seizure*, and *secondarily generalized seizure* have been eliminated from the official classification; however, they are still commonly used to describe seizures.
   2. Generalized onset seizures engage or involve networks on both sides of the brain at the onset. Can be classified as nonmotor or motor type
      a. Nonmotor (absence) seizures:
         i. Typical nonmotor seizures are brief and abrupt, last 10–30 seconds, and occur in clusters. They usually result in a short loss of consciousness, or patients may stare, be motionless, or have a distant expression on their face. Electroencephalograms (EEGs) during seizure activity usually show 3-Hz spike-and-wave complexes.
         ii. Other nonmotor seizure classifications include typical, atypical, myoclonic, and eyelid myoclonia.
      b. Motor: Myoclonic seizures: Consist of brief, rapid jerking movements of the entire body or the upper body and occasionally the lower extremities. Motor myoclonic-type seizures can further be classified as myoclonic, myoclonic atonic, or myoclonic tonic.
      c. Tonic-clonic seizures: Typically has five phases: flexion, extension, tremor, clonic, and postictal. During the flexion phase, the patient's mouth may be held partly open, and the patient may have upward eye movement, involvement of the extremities, and loss of consciousness. In the extension phase, patients may be noted to extend their back and neck; have contraction of the thoracic and abdominal muscles; be apneic; and have flexion, extension, and adduction of the extremities. The patient may cry out as air is forced from the lungs in this phase. The tremor phase occurs as the patient goes from tonic rigidity to tremors and then to a clonic state. During the clonic phase, the patient will have rhythmic jerks. The entire seizure usually lasts 1–3 minutes. After the seizure, the patient may be postictal. During this time, the patient can be difficult to arouse or very somnolent. Before the seizure, a patient may have a prodrome but not an aura.
      d. Clonic seizures: Only the clonic phase of a motor tonic-clonic seizure; rhythmic, repetitive, jerking muscle movements
      e. Tonic seizures: Only the flexion or extension phases of a motor tonic-clonic seizure
      f. Atonic seizures: Characterized by a loss of muscle tone. Motor-atonic seizures are often described as drop attacks, in which a patient loses tone and falls to the ground.

3. Seizures of unknown onset: Seizure onset cannot be determined as focal or generalized.
   a. Motor
   b. Nonmotor
   c. Unclassified
4. Epilepsy is a disease of the brain defined by any of the following conditions:
   a. Two unprovoked (or reflex) seizures occurring more than 24 hours apart;
   b. One unprovoked (or reflex) seizure and a probability of subsequent seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years;
   c. Diagnosis of an epilepsy syndrome (Epilepsia 2014;55:475-82)
5. Status epilepticus is caused either by the failure of the mechanisms responsible for seizure termination or by the initiation of mechanisms, which lead to abnormally prolonged seizures after 5 minutes. At this point, treatment for status epilepticus should be initiated. After 30 minutes, status epilepticus can have long-term consequences, including neuronal death, neuronal injury, and alteration of neuronal networks (depending on the type and duration of seizures). Mortality is up to 20% for status epilepticus (Epilepsia 2015;56:1515-23).
6. Nonepileptic seizures are paroxysmal nonepileptic episodes (according to EEG) resembling epileptic seizures that can be organic or psychogenic.
7. Other associated symptoms
   a. Prodrome: Awareness of an impending seizure before it occurs. The prodrome may consist of headache, insomnia, irritability, or a feeling of impending doom.
   b. Aura: A focal seizure, without loss of consciousness, consisting of sensory or autonomic symptoms that may precede evolution to a bilateral, convulsive seizure. Patients may have feelings of fear, embarrassment, or déjà vu. Automatic behavior (automatism) and psychic symptoms may occur. Automatisms may include lip smacking, chewing, swallowing, abnormal tongue movements, scratching, thrashing of the arms or legs, fumbling with clothing, and snapping the fingers. Psychic symptoms include illusions, hallucinations, emotional changes, dysphasia, and cognitive problems.

C. Diagnosis
1. Physical examination should occur, with special attention given to neurologic findings. The neurologic examination may include examination of the head, vision, cranial nerves, motor function, cerebellar function, and sensory function.
2. Laboratory tests are based on the patient's history and physical examination results; a full diagnostic panel is unnecessary in many patients. Because metabolic causes of seizures are common, serum glucose, electrolytes, calcium, CBCs, and renal function tests may be necessary. A toxicology screen may also be prudent.
3. EEGs are used to help confirm the diagnosis, classify seizures, locate the site of the seizures, and select the best seizure medication. The best time for an EEG is while the patient is having seizures. If doing an EEG is not possible during seizures, the EEG should be done as soon after the seizure as possible. Depending on the clinical situation, an EEG may be obtained under normal conditions, when the patient is sleep deprived, or when the patient is asleep. Patients whose seizures are difficult to diagnose or control may need prolonged video-EEG monitoring or ambulatory EEG. Although an interictal (when the patient is not having clinical seizures) EEG may be normal, this does not preclude the diagnosis of epilepsy.
4. MRI is the neuroimaging technique of choice for epilepsy. CT scanning can reveal brain lesions when an MRI cannot be done in a timely fashion.

D. Treatment
   1. Medications (see Tables 1–4)
      a. Benzodiazepines
         i. Mechanism of action: Augment γ-aminobutyric acid (GABA)-mediated chloride influx
         ii. Tolerance may develop: Usually used as adjunctive, short-term therapy
         iii. Most commonly used agents: Clorazepate (Tranxene), clobazam (Onfi, Sympazan), clonazepam (Klonopin), diazepam (Valium), and lorazepam (Ativan)
         iv. All benzodiazepines are controlled substances, scheduled as C-IV.
         v. For acute repetitive seizures: Intranasal midazolam (Nayzilam), intranasal diazepam (Valtoco), rectal diazepam (Diastat)
         vi. Nonepileptic indications: Clorazepate (anxiety disorders, anxiety), clonazepam (panic disorder with or without agoraphobia), lorazepam (anxiety disorders, anxiety, alcohol withdrawal)
      b. Brivaracetam (Briviact)
         i. Mechanism of action: Unknown mechanism, but has high affinity for synaptic vesicle protein 2A
         ii. Adverse effects: Somnolence, sedation, dizziness, fatigue
         iii. Drug interactions: Carbamazepine, phenobarbital, phenytoin
      c. Cannabidiol (Epidiolex)
         i. The only FDA-approved cannabis product for epilepsy
         ii. Approved for seizures caused by Dravet syndrome, tuberous sclerosis, and Lennox-Gastaut syndrome
         iii. Adverse effects: Sedation, drowsiness, diarrhea, intestinal cramping, increased liver transaminase (11% of patients); cannabidiol for 3% of patients is discontinued because of increased liver function tests
         iv. Metabolized by CYP2C19 and CYP3A4
         v. Inhibitor of UGT1A9, UGT2B7, CYP2C8, CYP2C9, CYP2C19
         vi. Possible inhibitor of CYP1A2, CYP2B6
         vii. Inhibits metabolism of desmethylclobazam, the active metabolite of clobazam
         viii. Increased hepatotoxicity with concomitant valproate
         ix. Maintenance dose: 10–20 mg/kg/day in two divided doses; initiate with 5 mg/kg/day in two divided doses and titrate to optimal dose
      d. Carbamazepine (Carbatrol, Epitol, Equetro, Tegretol, Teril)
         i. Mechanism of action: Fast sodium channel blocker
         ii. Pharmacokinetics: Enzyme inducer, autoinduction
         iii. Adverse effects: Rash (occurs after a delay of 2–8 weeks), syndrome of inappropriate antidiuretic hormone release, aplastic anemia, thrombocytopenia, anemia, leukopenia, hyponatremia
         iv. Carbamazepine toxicity symptoms: drowsiness, slurred speech, ataxia, hallucinations, nausea, vomiting, double vision, tremors, seizures, oliguria, and blurred vision
         v. Extended-release tablets (Tegretol XR) 100, 200, and 400 mg; extended-release capsules (Carbatrol) 100, 200, and 300 mg available. Dosing is still twice daily. Do not crush or chew. Extended-release capsules (Carbatrol) can be opened and sprinkled on food. Ghost tablets can occur in the stool with the extended-release tablets (Tegretol XR).
         vi. Patients with the *HLA-B*1502* allele have a 10-fold elevated risk of Stevens-Johnson syndrome.
            (a) Testing is recommended for Asian populations (including Asian Indian populations).
            (b) More than 15% of populations in Hong Kong, Malaysia, the Philippines, and Thailand have this allele.
         vii. Patients with the *HLA-A*3101* allele have a 12-fold elevated risk of hypersensitivity syndrome and a 3-fold elevated risk of maculopapular exanthema.
            (a) Prevalence of this allele is 2%–5% in northern European populations and 9.1% in Japanese populations.

(b) No recommendations have been issued for testing for this allele.

viii. Nonepileptic indication: Trigeminal neuralgia

e. Cenobamate (Xcopri)
   i. Mechanism of action: Inhibits voltage-gated sodium channels, modulates GABA receptors
   ii. Titrate slowly because of DRESS (drug rash with eosinophilia and systemic symptoms).
   iii. Contraindications: Familial short QT syndrome
   iv. Adjust dosing with renal function.
   v. CYP3A4 inducer; CYP2C19 inhibitor
   vi. Schedule V drug

f. Eslicarbazepine acetate (Aptiom)
   i. Mechanism of action: Fast sodium channel blocker
   ii. Prodrug for eslicarbazepine, with active metabolites; *R*-licarbazepine 5%, oxcarbazepine 1%
   iii. Adverse effects: Similar to those of carbamazepine; possibly reduced risk of rash, aplastic anemia, thrombocytopenia, and leukopenia
   iv. Adjust dose if CrCl is less than 50 mL/minute.

g. Ethosuximide (Zarontin)
   i. Mechanism of action: T-type calcium current blocker
   ii. Useful only for absence seizures
   iii. Adverse effects: Anorexia, gastric upset, nausea, vomiting, epigastric/abdominal pain, drowsiness, leukopenia, agranulocytosis, pancytopenia

h. Felbamate (Felbatol)
   i. Mechanism of action: Blocks glycine site on *N*-methyl-D-aspartate receptor
   ii. Serious adverse effects: Hepatotoxicity, aplastic anemia. Patient or guardian must sign consent form.
   iii. Uses: Only when seizures are severe and refractory to other medications and when the benefit clearly outweighs the potential adverse effects

i. Fenfluramine (Fintepla)
   i. Mechanism of action for seizures: Unknown
   ii. Indication: Seizures caused by Dravet syndrome in individuals older than 2 years
   iii. Warnings: Valvular heart disease, pulmonary arterial hypertension
   iv. Only available through a Risk Evaluation and Mitigation Strategies (REMS) program
   v. Increased risk of serotonin syndrome when used in combination with other serotonergic agents

j. Fosphenytoin (Cerebyx)
   i. Mechanism of action: Prodrug for phenytoin; fast sodium channel blocker
   ii. Uses: Parenteral formulation for loading or maintenance dosing in place of phenytoin; status epilepticus
   iii. Pharmacokinetics: Enzyme inducer, nonlinear kinetics
   iv. Dosing: Phenytoin equivalents (PE) (1.5 mg of fosphenytoin is equivalent to 1 mg of phenytoin sodium or 1 PE) are used. Loading dose: 10–20 mg of PE/kg intravenous or intramuscular dosing is appropriate. Maintenance dosage: Begin with 4–6 mg PE/kg/day in divided doses after administration of the loading dose.
   v. Adverse effects: Hypotension, perianal itching, other adverse effects of phenytoin
   vi. Advantages over phenytoin
      (a) Intramuscular or intravenous dosing
      (b) Phlebitis is minimized.
      (c) Infusion can be up to 150 mg PE per minute. In status epilepticus, infusion should be at 100–150 mg PE per minute. Maximum infusion rate is not to exceed 150 mg PE per minute because of the risk of severe hypotension and cardiac arrhythmias.
      (d) Can deliver in normal saline solution or 5% dextrose in water injection

k. Gabapentin (Neurontin)
   i. Mechanism of action: Inhibition of α2δ subunit of voltage-dependent calcium channels
   ii. Pharmacokinetics: Not metabolized, eliminated renally; adjustments may be necessary for renal dysfunction and hemodialysis
   iii. Nonepileptic indication: Postherpetic neuralgia pain
   iv. Doses often exceed product information maximum of 3600 mg/day.
   v. Extended-release tablets (Gralise) 300 and 600 mg are available. Their indication is for postherpetic neuralgia, not epilepsy.
   vi. Gabapentin enacarbil (Horizant) extended-release tablets 300 and 600 mg are available. This is a prodrug for gabapentin and is indicated for postherpetic neuralgia and restless legs syndrome, not epilepsy.
   vii. Increased risk of sedation and respiratory depression when used in combination with other sedating medications or opioids
l. Ganaxolone (Ztalmy)
   i. Indicated for the treatment of seizures associated with cyclin-dependent kinase-like deficiency disorder in patients 2 years and older
   ii. Mechanism of action: Positive modulation of the $GABA_A$ receptor in the CNS
   iii. Dosage form: Oral suspension 50 mg/mL
   iv. Dosing: Orally three times daily with food, titrated slowly
      (a) Dosage for patients weighing 28 kg or less:
         (1) The starting dosage is 6 mg/kg three times daily (18 mg/kg/day) for days 1–7; then:
         (2) 11 mg/kg three times daily (33 mg/kg/day) for days 8–14; then
         (3) 16 mg/kg three times daily (48 mg/kg/day) for days 15–21; then
         (4) Maximum dosage is 21 mg/kg three times daily (63 mg/kg/daily) on day 22 to ongoing.
      (b) Dosage for patients weighing over 28 kg:
         (1) The starting dosage is 150 mg three times daily (450 mg daily) for days 1–7; then
         (2) 300 mg three times daily (900 mg daily) for days 8–14; then
         (3) 450 mg three times daily (1350 mg daily) for days 15–21; then
         (4) Maximum dosage is 600 mg three times daily (1800 mg daily) on day 22 to ongoing.
   v. Adverse reactions: Somnolence, pyrexia, salivary hypersecretion, and seasonal allergy
   vi. Controlled substance scheduled C-V because of euphoric effects
   vii. Drug interactions: CYP3A4 inducers will decrease ganaxolone exposure. It is recommended to avoid concomitant use with strong or moderate CYP3A4 inducers; if unavoidable, consider a dosage increase, but do not exceed the maximum recommended dosage.
m. Lacosamide (Vimpat)
   i. Mechanism of action: Slow sodium channel blocker
   ii. Maximum dose is 300 mg/day with a CrCl of 30 mL/minute or less or with mild to moderate hepatic impairment.
   iii. Adverse effects: PR interval prolongation or first-degree atrioventricular block; baseline and steady-state ECG recommended in patients with known cardiac conduction problems, taking medications known to induce PR interval prolongation, or with severe cardiac disease
   iv. Controlled substance scheduled C-V because of euphoric effects
   v. Parenteral formulation: Has an FDA indication only for replacement of oral formulation; however, may be used for status epilepticus
n. Lamotrigine (Lamictal)
   i. Mechanism of action: Decreases glutamate and aspartate release, delays repetitive firing of neurons, blocks fast sodium channels

ii. Adverse effects: Rash is a primary concern because of concern for progression to Stevens-Johnson syndrome or toxic epidermal necrolysis; lamotrigine must be titrated slowly to avoid a rash.
iii. Valproic acid decreases lamotrigine metabolism (increases the serum concentration of lamotrigine); this interaction requires lower starting and final doses.
iv. Estrogen-containing oral contraceptives increase lamotrigine clearance, so twice the amount of lamotrigine may be necessary. Lamotrigine toxicity has been reported during the end of placebo week of oral contraceptive use.
v. Extended-release tablets (Lamictal XR) are available (25 mg, 50 mg, 100 mg, 200 mg, 250 mg, 300 mg).
vi. Nonepileptic indications: Maintenance treatment of type I bipolar disorder

o. Levetiracetam (Keppra)
i. Mechanism of action: May prevent hypersynchronization of epileptiform burst firing and propagation of seizure activity through binding at SV2A receptor
ii. Pharmacokinetics: Not metabolized extensively; adjust dose in renal dysfunction; no drug interactions with other seizure medications
iii. Adverse effects: Drowsiness, behavioral changes, depression, agitation, and coordination difficulties
iv. Parenteral use: Currently FDA indicated only for replacement of oral dosing; however, may be used for status epilepticus
v. Extended-release tablets (500 mg, 750 mg) are available for once-daily dosing.

p. Oxcarbazepine (Trileptal)
i. Mechanism of action: Fast sodium channel blocker
ii. Pharmacokinetics: Active metabolite 10-monohydroxy oxcarbazepine; enzyme inducer, no autoinduction
iii. Drug interactions: Enzyme inducer, decreases effectiveness of hormonal contraceptives
iv. Adverse effects: Hyponatremia more common than with carbamazepine (increased dose and advanced age increase risk of hyponatremia); blood dyscrasias less common than with carbamazepine; 25%–30% of patients with hypersensitivity to carbamazepine will have hypersensitivity to oxcarbazepine; rash
v. Extended-release tablets (Oxtellar XR) are available (150 mg, 300 mg, 600 mg).

q. Perampanel (Fycompa)
i. Mechanism of action: Noncompetitive antagonist of the inotropic α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) glutamate receptor
ii. Pharmacokinetics: 95%–96% protein bound to albumin and α_1-acid glycoprotein; metabolized by CYP3A4 and CYP3A5; 105-hour half-life
iii. Adverse effects: Neuropsychiatric effects (irritability, aggression, anger, anxiety), dizziness, gait disturbance, weight gain
iv. Perampanel is a schedule III controlled substance.

r. Phenobarbital (Luminal)
i. Mechanism of action: Increases GABA-mediated chloride influx
ii. Pharmacokinetics: Enzyme inducer
iii. Adverse effects: Hyperactivity, cognitive impairment
iv. Phenobarbital is a schedule IV controlled substance.
v. Nonepileptic use: Anxiety, severe alcohol withdrawal

s. Phenytoin (Dilantin, Phenytek)
i. Mechanism of action: Fast sodium channel blocker
ii. Pharmacokinetics: Enzyme inducer, nonlinear kinetics

iii. Administration considerations
  (a) Intravenous formulation: Very basic product. Phlebitis and extravasation are concerns; hypotension; maximal infusion rate of 50 mg/minute because of risk of cardiac arrhythmias and hypotension. Can prepare only in normal saline solution
  (b) Oral suspension: Must be shaken well; adheres to feeding tubes and is bound by enteral nutrition products
iv. Dose-related adverse effects: Nystagmus, ataxia, drowsiness, cognitive impairment
v. Non–dose-related adverse effects: Gingival hyperplasia, hirsutism, acne, rash, hepatotoxicity, coarsening of facial features

t. Pregabalin (Lyrica)
i. Mechanism of action: Inhibition of α2δ subunit of voltage-dependent calcium channels
ii. Pharmacokinetics: Not metabolized, renally excreted; reduce dose in renal dysfunction
iii. Adverse effects: Drowsiness, blurred vision, weight gain, edema, angioedema, CK elevations (three reports of rhabdomyolysis), rash
iv. Schedule V controlled substance: Insomnia, nausea, headache, diarrhea reported after abrupt discontinuation; gradually discontinue over at least 1 week
v. Nonepileptic indications: Neuropathic pain associated with diabetic neuropathy, postherpetic neuralgia, spinal cord injury, generalized anxiety disorder, and fibromyalgia
vi. Increased risk of sedation and respiratory depression when used in combination with other sedating medications or opioids

Table 1. Medication Selection for Various Seizure Types[a]

Medication	Focal	Generalized Motor	Absence	Atonic	Myoclonic	Infantile Spasms	Dravet Syndrome	Lennox-Gastaut Syndrome
Brivaracetam	3	—	—	—	—	—	—	—
Cannabidiol	—	—	—	—	—	—	3	3
Carbamazepine	1	1	—	4	4	—	—	—
Cenobamate	4	—	—	—	—	—	—	—
Clobazam	4	4	3	—	3	—	2	1
Clonazepam	3	3	2	1	2	2	—	1
Diazepam	—	—	—	—	4	4	—	2
Eslicarbazepine	4	—	—	—	—	—	—	—
Ethosuximide	—	—	1	—	4	—	—	—
Felbamate	5	5	5	—	5	—	—	5
Fenfluramine	—	—	—	—	—	—	5	—
Gabapentin	1	2	—	—	—	—	—	—
Lacosamide	1	—	—	—	—	—	—	—
Lamotrigine	1	1	2	3	3	—	—	1
Levetiracetam	1	1	4	—	3	—	1	—
Lorazepam	3	3	3	—	3	—	—	—
Oxcarbazepine	1	1	—	3	3	—	—	—
Perampanel	4	—	—	—	—	—	—	—
Phenobarbital	2	2	2	—	3	—	—	—
Phenytoin	2	2	—	—	3	—	—	—
Pregabalin	4	—	—	—	—	—	—	—
Primidone	2	2	2	—	—	—	—	—
Rufinamide	4	3	3	3	—	—	—	1

Table 1. Medication Selection for Various Seizure Types[a] (*Cont'd*)

Medication	Focal	Generalized Motor	Absence	Atonic	Myoclonic	Infantile Spasms	Dravet Syndrome	Lennox-Gastaut Syndrome
Stiripentol	—	—	—	—	—	—	6	—
Tiagabine	4	—	—	4	4	—	—	—
Topiramate	1	1	3	3	1	—	—	4
Valproic acid	2	1	1	1	1	1	2	—
Vigabatrin	5	5	—	—	—	5	—	—
Zonisamide	1	3	3	—	4	—	—	—

[a]Not all uses are FDA-approved indications.

1 = first-line agent; 2 = second-line agent; 3 = some therapeutic effect; 4 = adjunctive therapy; 5 = used only when benefits outweigh risks; 6 = in combination with clobazam.

Table 2. Selected Interactions of Non–Antiseizure Medications on Seizure Medications

Seizure Medication	Other Medication	Effect on the Seizure Medication	Mechanism
Carbamazepine	Cimetidine	Increased serum concentration	Inhibition of carbamazepine metabolism
	Diltiazem	Increased serum concentration	Inhibition of carbamazepine metabolism
	Erythromycin	Increased serum concentration	Inhibition of carbamazepine metabolism
	Isoniazid	Increased serum concentration	Inhibition of carbamazepine metabolism
	Nefazodone	Increased serum concentration	Inhibition of carbamazepine metabolism
	Theophylline	Decreased serum concentration	Increased carbamazepine metabolism
	Verapamil	Increased serum concentration	Inhibition of carbamazepine metabolism
Clobazam	Fluconazole	Increased serum concentration	Inhibitor of CYP2C19
	Fluvoxamine	Increased serum concentration	Inhibitor of CYP2C19
	Omeprazole	Increased serum concentration	Inhibitor of CYP2C19
Gabapentin	Antacids	Decreased serum concentration	Decreased bioavailability
Lamotrigine	Estrogen-containing contraceptives	Decreased serum concentration	Possibly induction of glucuronidation of lamotrigine
	Rifampin	Decreased serum concentration	Possibly induction of glucuronidation of lamotrigine
Perampanel	Ethanol and other CNS depressants	CNS additive or supra-additive effects	Additive CNS depression
	Rifampin	Decreased serum concentration	Increased metabolism
	St. John's wort	Decreased serum concentration	Increased metabolism
Phenobarbital; primidone	Ethanol	Acute ethanol ingestion may cause CNS additive effects and respiratory depression; chronic ethanol ingestion may result in variable effects	Additive CNS depression and decreased barbiturate metabolism with acute ethanol ingestion

Table 2. Selected Interactions of Non–Antiseizure Medications on Seizure Medications (*Cont'd*)

Seizure Medication	Other Medication	Effect on the Seizure Medication	Mechanism
Phenytoin	Anticoagulants, oral	May increase phenytoin serum concentration; decreased or increased anticoagulant effects	Complex mechanism
	Antineoplastics (bleomycin, cisplatin, vinblastine, methotrexate, carmustine)	Decreased pharmacologic effect	Unknown, possible decreased absorption caused by antineoplastic mucosal damage
	Chloramphenicol	Increased phenytoin serum concentration; decreased or increased chloramphenicol serum concentration	Inhibition of phenytoin metabolism; effect on chloramphenicol unknown
	Cimetidine	Increased serum concentration	Inhibition of phenytoin metabolism
	Diazoxide	Decreased pharmacologic effect; decreased serum concentration	Increased phenytoin metabolism
	Diltiazem	Increased serum concentration	Inhibition of phenytoin metabolism
	Disulfiram	Increased serum concentration	Inhibition of phenytoin metabolism
	Folic acid	Decreased serum concentration	Complex mechanism
	Isoniazid	Increased serum concentration	Inhibition of phenytoin metabolism
	Phenylbutazone	Increased serum concentration	Inhibition of phenytoin metabolism; plasma protein displacement
	Rifampin	Decreased serum concentration	Increased phenytoin metabolism
	Sulfonamides	Increased serum concentration	Inhibition of phenytoin metabolism
	Trimethoprim	Increased serum concentration	Inhibition of phenytoin metabolism
Topiramate	Hydrochlorothiazide	Increased serum concentration	Unknown
Valproic acid	Estrogen-containing oral contraceptives	Decreased serum concentration	Possibly induction of glucuronidation of lamotrigine
	Meropenem	Decreased serum concentration	Increased valproic acid metabolism
	Rifampin	Decreased serum concentration	Increased valproic acid metabolism
	Salicylates	Increased pharmacologic effect	Plasma protein displacement; increased free valproic concentration

Table 3. Pharmacokinetic Parameters of Seizure Medications When Used as Monotherapy

Medication	Therapeutic Serum Concentration (mcg/mL)	Bioavailability (%)	Plasma Protein Binding (%)	Volume of Distribution (L/kg)	Eliminated Unchanged (%)	Clinically Active Metabolites	Half-Life (hr)	Level of Recommendation to Use Therapeutic Serum Concentration[a]
Brivaracetam	0.5–0.9	> 90	< 20	0.5	< 10	None	9	3
Cannabidiol	Not established	< 20, significantly increased with fatty meal	> 94	232–535	Little, if any	7-hydroxy-cannabidiol	56–61	–
Carbamazepine	4–12 mcg/mL	> 70	40–90	0.8–1.9 1.5 (neonates) 1.9 (children)	Little, if any	10,11-epoxide	12–17 8–14 (children)	1
Cenobamate	Not established	85–90	60	0.5–0.7	< 10	None	50–60	–
Clobazam	30–300 ng/mL	100	80–90	100	3	*N*-desmethylclobazam	36–2 71–82 (*N*-desmethylclobazam)	3
Clonazepam	20–80 ng/mL	100	47–80	3.2	Low percentage	7-amino, low activity	19–50 22–33 (children)	3
Eslicarbazepine	10–35	90	< 40	0.87	90	*R*-licarbazepine, oxcarbazepine	13–20	3
Ethosuximide	40–100	100	21.8	0.6–0.7	10–20	None	52–60 24–36 (children)	3
Felbamate	30–60[b]	> 90	22–36	0.74–0.85	40–50	None	11–20 13–23 (children)	3
Fenfluramine	1–10	68–74	50	12	< 25	Norfenfluramine	20	–
Gabapentin	2–20[b]	Dose-dependent	< 3	0.65–1.04	75–80	None	5–7	3
Ganaxolone	Not established	> 90	99	0.8	2	None	34	–
Lacosamide	1–10	100	< 15	0.6	40	None	13	3
Lamotrigine	1–13	98	55	0.9–1.2	10	None	12–55 24–30 (children)	2
Levetiracetam	12–46[b]	100	< 10	0.5–0.7	66	None	7 5 (children)[c]	4
Oxcarbazepine	3–35[b]	100[c]	67	0.7	< 1	10-monohydroxy	9	2
Perampanel	180–980	100	95–96	—	20–36	None	105	3
Phenobarbital	15–40	80–100	40–60	0.7–1	25	None	80–100 45–173 (neonates) 37–73 (children)	1
Phenytoin	10–20	85–95	> 90	0.6–0.8	< 5	None	~20[d] 10–140 (neonates)[d] 5–18 (children)[d]	1
Pregabalin	2–5	≥ 90	0	0.5	90	None	6	3
Primidone	Primidone	90–100	80	0.6	20–40	Phenobarbital PEMA	10–15; 17 (PEMA) 4.5–18 (children) 10–36 (PEMA; children)	2
Rufinamide	5–30	85	34	50[f]	2	None	6–10	2
Stiripentol	1–10	Not determined	99	3.2	< 10	None	4.5–13; increases with increasing dose	2
Tiagabine	0.02–0.2[b]	90–95	96	1.2	—	None	3.2–5.7	2
Topiramate	Topiramate	80	13–17	0.6–0.8	70	None	12–21	3
Valproic acid	40–100 (150)[e]	100	> 90[g]	0.2	< 5	Unknown	8–17 4–14 (children)	1
Vigabatrin	2–10	100	0	1.1	80	None	7.5 5.7 (infants)	4
Zonisamide	10–40	50	40	1.45	35	None	63	2

[a]1 = strongly recommended; 2 = recommended; 3 = useful; 4 = potentially useful.

[b]Therapeutic serum concentrations not well established.

[c]Bioavailability decreased in children < 8 yr and in older adults; clearance is 80% higher in children 2–4 yr and 40% higher in children 4–12 yr than in adults.

[d]Michaelis-Menten pharmacokinetics; half-life varies with serum concentration; therefore, it might be better to express phenytoin elimination in the length of time it takes to clear 50% of the drug from the body, for example.

[e]Upper end of the serum concentration range is not definitely established.

[f]Depends on dose.

[g]May vary with serum concentration.

NAMR = *N*-acetyl metabolite of ezogabine; PEMA = phenylethylmalonamide.

u. Primidone (Mysoline)
    i. Mechanism of action: Increases GABA-mediated chloride influx
    ii. Metabolized to phenobarbital and phenylethylmalonamide
    iii. Adverse effects: Sedation, drowsiness, ataxia, rash
    iv. Primidone, phenobarbital, and phenylethylmalonamide all have antiepileptic action.
    v. Pharmacokinetics: Enzyme inducer
    vi. Also used for essential tremor
v. Rufinamide (Banzel)
    i. Mechanism of action: Fast sodium channel blocker
    ii. Pharmacokinetics: Absorption increased by food (should be administered with food); metabolized by hydrolysis rather than through CYP enzymes
    iii. Adverse effects: Headache, dizziness, fatigue, somnolence, nausea
    iv. Decreases concentrations of ethinyl estradiol and norethindrone
    v. Has an FDA indication only for Lennox-Gastaut syndrome
    vi. Slightly shortens the QT interval and therefore should not be used in patients with familial short QT syndrome
    vii. Available as an oral solution
w. Stiripentol (Diacomit)
    i. Indicated for Dravet syndrome in combination with clobazam
    ii. Dose: 50 mg/kg/day in two or three divided doses
    iii. Adverse effects: Somnolence, decreased appetite, agitation, ataxia, weight loss, hypotonia, nausea, tremor, dysarthria, insomnia
    iv. Pharmacokinetics: Inhibits CYP 1A2, 2C19, 2D6, and 3A4
x. Tiagabine (Gabitril)
    i. Mechanism of action: Blocks GABA reuptake in the presynaptic neuron
    ii. Associated with new-onset seizures and status epilepticus in patients without epilepsy
    iii. Adverse effects: Dizziness, asthenia, somnolence, nervousness, tremor, diarrhea
y. Topiramate (Topamax)
    i. Mechanism of action: Fast sodium channel blocker, enhances GABA activity and antagonizes AMPA/kainate activity, weak carbonic anhydrase inhibitor
    ii. Pharmacokinetics: Not extensively metabolized, eliminated in urine
    iii. Adverse effects: Drowsiness, paresthesias, psychomotor slowing (titrate slowly), weight loss, nephrolithiasis, acute angle-closure glaucoma, metabolic acidosis, hyperthermia (associated with decreased perspiration, or oligohidrosis), and decreased cognition, including word-finding difficulties
    iv. Extended-release formulations (Trokendi XR, Qudexy XR)
    v. Nonepileptic indication: Prophylaxis of migraine headaches, weight loss secondary to antipsychotic use
z. Valproic acid, divalproex sodium, valproate (Depacon, Depakene, Depakote, Stavzor)
    i. Mechanism of action: Blocks T-type calcium currents, blocks sodium channels, increases GABA production
    ii. Pharmacokinetics: Enzyme inhibitor
    ii. Parenteral use: Has FDA indication only for replacement of oral dosing; however, sometimes used for status epilepticus, especially if absence status epilepticus
    iv. Adverse effects: Hepatotoxicity, nausea and vomiting, weight gain, interference with platelet aggregation, pancreatitis, alopecia, tremor

v. Available in immediate-release (valproic acid [Depakene]) capsules for three- or four-times-daily dosing; delayed-release (enteric coated) (divalproex sodium [Depakote], valproic acid [Stavzor]) capsules and tablets for twice-daily dosing (if patient is taking an enzyme inducer, agent is dosed more often); and extended-release (divalproex sodium [Depakote ER]) tablets for once-daily dosing
vi. Nonepileptic indications: Manic episodes associated with bipolar disorder, prophylaxis of migraine headaches

aa. Vigabatrin (Sabril)
i. Mechanism of action: Irreversible inhibition of GABA transaminase
ii. Pharmacokinetics: Induces CYP2C9; renal elimination; dose adjustment required for CrCl less than 60 mL/minute
iii. Adverse effects: Fatigue, somnolence, nystagmus, tremor, blurred vision, vision impairment, weight gain, arthralgia, abnormal coordination, and confusional state
iv. Serious adverse effect: Vision loss; increased risk with higher total dose and duration; periodic vision testing necessary; restricted distribution program; only used for refractory complex partial seizures and infantile spasms
v. Only available through a REMS program
vi. Available as oral powder for solution

bb. Zonisamide (Zonegran)
i. Mechanism of action: Fast sodium channel blocker, blocks T-type calcium currents, weak carbonic anhydrase inhibitor
ii. Non-arylamine sulfonamide: Avoid in patients with sulfa sensitivity; sometimes used in patients with nonserious sulfa allergies, particularly when non-acrylamides (i.e., sulfonylureas) have been used successfully
iii. Pharmacokinetics: Long half-life, renal elimination
iv. Adverse effects: Depression, rash, psychomotor slowing, paresthesias, kidney stones, blood dyscrasias, hyperthermia (associated with decreased perspiration, or oligohidrosis), metabolic acidosis

Table 4. Starting and Maximal Adult Seizure Medication Doses

Medication	Starting Dose	Usual Maximal Dose
Brivaracetam	50 mg twice daily	200 mg/day
Cannabidiol	2.5 mg/kg twice daily	10 mg/kg twice daily
Carbamazepine	200 mg twice daily	1600 mg/day
Cenobamate	12.5 mg/day	400 mg/day
Clobazam	10 mg/day	40 mg/day
Clonazepam	0.5 mg three times/day	20 mg/day
Eslicarbazepine	400 mg/day	1200 mg/day
Ethosuximide	250 mg twice daily	1.5 g/day
Felbamate	400 mg three times/day	3600 mg/day
Fenfluramine	0.1 mg/kg twice daily	0.35 mg/kg twice daily to maximum of 26 mg/day; with stiripentol, 0.2 mg/kg twice daily to maximum of 17 mg/day
Gabapentin	300 mg three times/day	3600 mg/day
Ganaxolone	Weight-based dosing (see text above)	Weight-based dosing (see text above)
Lacosamide	50 mg twice daily	400 mg/day

Table 4. Starting and Maximal Adult Seizure Medication Doses (*Cont'd*)

Medication	Starting Dose	Usual Maximal Dose
Lamotrigine	With valproic acid: 25 mg every other day Without carbamazepine, phenytoin, phenobarbital, primidone, or valproic acid: 25 mg/day With carbamazepine, phenytoin, phenobarbital, or primidone and not with valproic acid: 50 mg/day	With valproic acid: 200 mg/day Without carbamazepine, phenytoin, phenobarbital, primidone, or valproic acid: 375 mg/day With carbamazepine, phenytoin, phenobarbital, or primidone and not with valproic acid: 500 mg/day
Levetiracetam	500 mg twice daily	3000 mg/day
Oxcarbazepine	300 mg twice daily	2400 mg/day
Perampanel	With enzyme-inducing seizure medications: 4 mg/day Without enzyme-inducing seizure medications: 2 mg/day	With enzyme-inducing seizure medications: 12 mg/day Without enzyme-inducing seizure medications: 8 mg/day
Phenobarbital	1–3 mg/kg/day	300 mg/day
Phenytoin	100 mg three times/day	600 mg/day
Pregabalin	75 mg twice daily	600 mg/day
Primidone	100 mg at bedtime	2000 mg/day
Rufinamide	200–400 mg twice daily	3200 mg/day
Stiripentol	50 mg/kg/day in two or three divided doses; must be administered with clobazam	3000 mg/day
Tiagabine	With carbamazepine, phenytoin, primidone, phenobarbital: 4 mg/day Without carbamazepine, phenytoin, primidone, phenobarbital: 2 mg/day	With carbamazepine, phenytoin, primidone, phenobarbital: 56 mg/day
Topiramate	25–50 mg/day	400 mg/day
Valproic acid	10–15 mg/kg/day	60 mg/kg/day
Vigabatrin	500 mg twice daily	3000 mg/day
Zonisamide	100 mg/day	600 mg/day

2. Surgery: Surgery can sometimes drastically reduce the number of seizures; possible surgical procedures include removal of the seizure focus, corpus callosotomy, or implantation of vagus nerve stimulators.
3. Status epilepticus
    a. Treatment principles
        i. Ascertain ABCs (airway, breathing, and circulation).
        ii. Laboratory values (fingerstick blood glucose, CBC, basic metabolic panel, calcium, magnesium, and seizure medication serum concentrations, if applicable) are sent to determine any reversible causes of status epilepticus.
        iii. If blood glucose is less than 60 mg/dL, administer thiamine 100 mg intravenously followed by dextrose 50%.
        iv. Administer an emergency medication to stop the seizure immediately.
        v. Follow with an urgent medication to prevent the recurrence of seizures.
        vi. In general, all medications for status epilepticus should be administered parenterally.
        vii. Neuromuscular-blocking drugs do not stop seizures; they stop only the muscular response to the brain's electrical activity.

b. Emergency medications
    i. Lorazepam: Drug of choice
        (a) Rapid onset (2–3 minutes)
        (b) Dosage 0.1 mg/kg (up to 4 mg/dose) at a rate of up to 2 mg/minute; may repeat every 5–10 minutes
    ii. Diazepam
        (a) Rapid onset, short duration
        (b) Dosage 0.15 mg/kg (up to 10 mg/dose) at a rate of up to 5 mg/minute. May repeat every 5 minutes
        (c) Rectal gel and intranasal formulations are available.
    iii. Midazolam: Preferred for intramuscular administration
        (a) Rapid onset, short duration
        (b) Dosage 0.2 mg/kg (up to 10 mg/dose). Can be administered intramuscularly, intranasally, or buccally
c. Urgent medications
    i. Phenytoin: Dosage 20 mg/kg; administration rate no more than 50 mg/minute
    ii. Fosphenytoin: Administration rate no more than 150 mg of PE per minute
    iii. Phenobarbital: Dosage 20 mg/kg at 50–100 mg/minute
    iv. Valproic acid: Dosage 20–40 mg/kg at up to 6 mg/kg/minute; does not have FDA-labeled approval for status epilepticus
    v. Levetiracetam: 40–60 mg/kg over 15 minutes (maximum 4.5 g/dose); does not have FDA-labeled approval for status epilepticus
    vi. Lacosamide: 200- to 400-mg bolus over 15 minutes; does not have FDA-labeled approval for status epilepticus
d. Refractory status epilepticus medications
    i. Benzodiazepine-resistant status epilepticus: Fosphenytoin = levetiracetam = valproate (N Engl J Med 2019;381:2103-13)
    ii. Pentobarbital: Load 5–15 mg/kg up to 50 mg/minute; follow with a 0.5- to 5-mg/kg/hour infusion.
        (a) May have severe hypotension, necessitating treatment with vasopressors; should have continuous blood pressure measurement
        (b) Must be on ventilator
    iii. Midazolam: Load 0.2-mg/kg infused up to 2 mg/minute; follow with a 0.05- to 2-mg/kg/hour infusion.
        (a) May have hypotension, respiratory depression
        (b) May have tachyphylaxis
    iv. Propofol: Load a 1- to 2-mg/kg intravenous bolus for 30–60 seconds; follow with a 20- to 200-mcg/kg/minute infusion.
        (a) Significant source of lipids
        (b) Some reports of seizure exacerbation with propofol
        (c) Must be on ventilator
        (d) PRIS (propofol infusion syndrome) with prolonged administration

4. Special populations
    a. Older adults: Pharmacokinetic changes in older adults that may affect seizure medications include the following:
        i. Carbamazepine: Decreased clearance
        ii. Phenytoin: Decreased protein binding if hypoalbuminemic or in renal failure
        iii. Valproic acid: Decreased protein binding
        iv. Diazepam: Increased half-life
        v. Phenylethylmalonamide (active metabolite of primidone): Decreased clearance if CrCl is decreased
        vi. Lamotrigine: Decreased clearance
        vii. Seizure medications with renal elimination must be adjusted according to the CrCl value.
    b. Women's health
        i. During their reproductive years, women with epilepsy should:
            (a) Take the best drug for their seizure type. Women of childbearing age should not be administered valproic acid unless other therapies have failed.
            (b) Be treated with monotherapy, if possible
            (c) Discuss the possible decrease in hormonal contraceptive effectiveness if taking enzyme-inducing medications (Table 5)
            (d) Use folic acid supplementation with no less than 0.4 mg/day
        ii. Three practice guidelines exist regarding epilepsy during pregnancy (relevant material excerpted in the text that follows).
            (a) Avoiding valproic acid monotherapy or polytherapy during the first trimester of pregnancy should be considered to decrease the risk of major congenital malformations, particularly neural tube defects, facial clefts, hypospadias, and poor cognitive outcomes. Valproic acid use has now been associated with lower IQ scores at ages 3 and 4½ years (Neurology 2012;78:1207-14).
            (b) To reduce the risk of major congenital malformations and poor cognitive outcomes, avoiding the use of seizure medication polytherapy during pregnancy, if possible, should be considered.
            (c) Limiting the dose of valproic acid (less than 700 mg/day), topiramate, or lamotrigine during the first trimester, if possible, should be considered to reduce the risk of major congenital malformations.
            (d) Avoiding the use of phenytoin, carbamazepine, and phenobarbital, if possible, may be considered to reduce the risk of cleft palate (phenytoin), posterior cleft palate (carbamazepine), cardiac malformations (phenobarbital), and poor cognitive outcomes (phenytoin, phenobarbital).
            (e) Women with epilepsy taking seizure medications during pregnancy probably have an elevated risk of small-for-gestational-age infants and 1-minute Apgar scores less than 7.
            (f) Monitoring of lamotrigine, carbamazepine, and phenytoin serum concentrations during pregnancy should be considered.
            (g) Monitoring of levetiracetam and oxcarbazepine (as the mono-hydroxylated derivative) serum concentrations during pregnancy may be considered.

Table 5. Effect of Seizure Medications on Hormonal Contraceptives

Seizure Medication	Oral Contraceptives, Contraceptive Patch, Contraceptive Vaginal Ring, Progestogen Implant	Medroxyprogesterone Acetate Depot Injection, Levonorgestrel-Releasing Intrauterine System
Brivaracetam Carbamazepine Cenobamate Clobazam Eslicarbazepine Felbamate Lamotrigine Oxcarbazepine Perampanel Phenobarbital Phenytoin Primidone Rufinamide Topiramate[a]	Decrease effectiveness	No effect
Benzodiazepines Cannabidiol Ethosuximide Fenfluramine Gabapentin Ganaxolone Lacosamide Levetiracetam Pregabalin Stiripentol Tiagabine Valproic acid Vigabatrin Zonisamide	No effect	No effect

[a]Doses > 200 mg/day.

E. Other Issues
   1. Initiating therapy after a first seizure
      a. Guidance from the American Epilepsy Society and the American Academy of Neurology
      b. Adults with an unprovoked first seizure (e.g., not meningitis, intoxication) will have a 21%–45% chance of having more seizures within the next 2 years. Higher risks are associated with prior brain insults, EEG with epileptiform abnormalities, and nocturnal seizures.
      c. Initiating antiseizure medication (ASM) therapy will probably reduce recurrence risk within the first 2 years but may not increase quality of life.
      d. Initiating ASM therapy early does not change the long-term risk of seizures.
   2. Driving: All states place driving restrictions on people with epilepsy; some require mandatory physician reporting to the state department of transportation.

3. Medication discontinuation
    a. The following criteria can be used to determine the possibility of withdrawal from ASM therapy:
        i. Patient should be seizure free for 2–5 years on seizure medication.
        ii. Patient should have a single type of focal or generalized seizures.
        iii. Patient should have a normal neurologic examination and normal IQ.
        iv. Patient's EEG should have normalized with seizure medication treatment.
    b. If a medication is discontinued, it is usually tapered for several months; a typical regimen would reduce the dose by one-third for 1 month, reduce it by another one-third for 1 month, and then discontinue it.
4. Monitoring
    a. Number of seizures: The goal number of seizures is always zero.
    b. Signs of toxicity
    c. Laboratory values: Specific for each agent
    d. Blood concentrations: Available for many of the medications; commonly used for carbamazepine, phenobarbital, phenytoin, and valproic acid. The ILAE has a position paper on therapeutic drug monitoring, giving situations in which serum concentrations are most likely beneficial:
        i. When a person has attained the desired clinical outcome, to establish an individual therapeutic concentration that can then be used to assess potential causes for a change in drug response
        ii. As an aid in diagnosing clinical toxicity
        iii. To assess adherence, particularly in patients with uncontrolled seizure or breakthrough seizures
        iv. To guide dosage adjustment in situations associated with increased pharmacokinetic variability (e.g., children, older adults, patients with associated diseases, drug formulation changes)
        v. When a potentially important pharmacokinetic change is anticipated (e.g., in pregnancy, or when an interacting drug is added or removed)
        vi. To guide dose adjustments for seizure medications with dose-dependent pharmacokinetics, particularly phenytoin
5. Sexual dysfunction
    a. Described in 30%–60% of men and women with epilepsy
    b. Includes hyposexuality, orgasmic dysfunction, and erectile dysfunction
    c. Mechanism may be induction of CYP isoenzymes to increase testosterone metabolism, increased hepatic synthesis of sex hormone–binding globulin, or induction of aromatase, which converts free testosterone to estradiol.
    d. Sexual dysfunction has been reported with carbamazepine, phenobarbital, phenytoin, pregabalin, topiramate, and zonisamide.
    e. Improved sexual functioning has been reported with lamotrigine and oxcarbazepine.
6. Bone health
    a. Osteopenia or osteoporosis is found in 38%–60% of patients in tertiary epilepsy clinics.
    b. Increased fractures in patients with epilepsy and with seizure medication use
    c. Risk is increased with increased treatment duration; there is a dose-response relationship; the medications most often associated with poor bone health are carbamazepine, clonazepam, phenobarbital, phenytoin, and valproic acid. However, evidence now suggests that all seizure medications contribute to osteopenia or osteoporosis.
    d. Proposed mechanisms: Hepatic induction of CYP isoenzymes leads to increased vitamin D catabolism, impaired calcium absorption, calcitonin deficiency, vitamin K interference, and direct harmful effects on bone cells.
    e. Proposed treatments: High-dose vitamin D (4000 international units/day for adults and 2000 international units/day for children) improves bone mineral density compared with low doses; estrogen may be helpful for women but may also trigger seizures in some women.

7. Suicidality
    a. Meta-analysis of 199 placebo-controlled clinical trials of 11 drugs (n=43,892 patients older than 5 years) showed that patients who received seizure medications had about twice the risk of suicidal behavior or ideation (0.43%) compared with patients receiving placebo (0.22%), and there were four completed suicides in the treatment group versus zero in the placebo group.
        i. Risk is increased at 1 week and continues through week 24.
        ii. Patients with epilepsy (RR 3.6), psychiatric disorders (RR 1.6), or other conditions (RR 2.3) were all at elevated risk of suicidality; no differences between drugs; no differences between age groups
    b. The FDA requires a warning and a medication guide for all seizure medications.
    c. Recent observational studies show mixed results. When specific ASMs are examined, those most associated with depression and suicidality are levetiracetam, perampanel, phenobarbital, primidone, tiagabine, topiramate, and vigabatrin.
    d. A 2013 expert consensus statement made the following points:
        i. Although some (but not all) ASMs can be associated with treatment-emergent psychiatric problems that may lead to suicidal ideation and behavior, the actual suicidal risk has not yet been established; however, it seems to be very low. The risk of discontinuing ASMs or refusing to initiate them is significantly worse and can result in serious harm, including patient death.
        ii. Suicidality in epilepsy is multifactorial. Primary operant variables include postictal suicidal ideation; a history of psychiatric disorders, particularly mood and anxiety disorders (and above all, when associated with prior suicide attempts); and a family history of mood disorder complicated by suicide attempts.
        iii. When initiating or changing ASMs, patients should be advised to report any changes in mood and suicidal ideation.
    e. Self-care seizure plans
        i. Train patients and caregivers on first aid for seizures.
        ii. Instruct on when patient should receive emergency care.
        iii. Provide seizure rescue medication (e.g., intranasal diazepam, intranasal midazolam).

Patient Cases

Questions 1–3 pertain to the following case.

T.M. is a 23-year-old woman with newly diagnosed generalized motor myoclonic-type seizures. She is in good health and takes oral contraceptives.

1. Which is the best medication for T.M.'s seizures?
    A. Valproate.
    B. Phenytoin.
    C. Phenobarbital.
    D. Levetiracetam.

2. T.M. is concerned about the impact of levetiracetam on her oral contraceptives. Which response is best?
    A. Levetiracetam does not alter the effectiveness of your oral contraceptives.
    B. You should use alternative forms of birth control because levetiracetam decreases oral contraceptive effectiveness.
    C. You may have breakthrough bleeding, but the effectiveness of the oral contraceptive is not changed.
    D. Oral contraceptives decrease the effectiveness of levetiracetam, so you need another form of birth control.

Patient Cases (*Cont'd*)

3. Three months later, T.M.'s seizures are reduced in frequency, but continue despite medication adherence and maximized dosing. Which would be the best alternative?
   A. Lamotrigine.
   B. Rufinamide.
   C. Cannabidiol.
   D. Valproate.

4. J.G. is a 34-year-old patient who presents to the ED in status epilepticus. All of her laboratory values are normal. Which medication is best to use first?
   A. Valproate.
   B. Lorazepam.
   C. Phenytoin.
   D. Phenobarbital.

5. S.R. is a 37-year-old patient who began taking phenytoin 100 mg 3 capsules orally at bedtime 6 months ago. He has had several seizures since then, the most recent of which occurred 7 days ago. At that time, his phenytoin serum concentration was 8 mcg/mL. The treating physician increased his phenytoin dose to 100 mg 3 capsules orally twice daily. Today, which best represents his expected serum concentration?
   A. 10 mcg/mL.
   B. 14 mcg/mL.
   C. 16 mcg/mL.
   D. 24 mcg/mL.

6. S.S. is a 7-year-old girl. Her teacher contacts the girl's parents because of concern about the girl's "daydreaming" in class. After an evaluation, S.S. is diagnosed with generalized nonmotor (absence) seizures. Which agent is best to treat this type of epilepsy?
   A. Phenytoin.
   B. Valproate.
   C. Carbamazepine.
   D. Ethosuximide.

7. J.B. is a 25-year-old man with a history of seizure disorder. He has been treated with carbamazepine for 1 year, and his current carbamazepine concentration is 12 mcg/mL. Which adverse effect is J.B. most likely to have with carbamazepine at this concentration?
   A. Hepatotoxicity.
   B. Acne.
   C. Gingival hyperplasia.
   D. Diplopia.

Patient Cases (*Cont'd*)

8. M.G. has been prescribed levetiracetam. On which adverse effect is it best to counsel M.G.?
   A. Hepatoxicity.
   B. Renal stones.
   C. Depression.
   D. Word-finding difficulties.

Questions 9 and 10 pertain to the following case.

G.Z., a 26-year-old woman, presents with a 6-month history of "spells." The spells are all the same, and all begin with a feeling in the abdomen that is difficult for her to describe. This feeling rises toward the head. The patient believes that she will then lose awareness. After a neurologic workup, she is diagnosed with focal seizures evolving to a bilateral, convulsive seizure. The neurologist is considering initiating either carbamazepine or oxcarbazepine.

9. Which is the most accurate comparison of carbamazepine and oxcarbazepine?
   A. Oxcarbazepine causes more liver enzyme induction than carbamazepine.
   B. Oxcarbazepine does not cause rash.
   C. Oxcarbazepine does not cause hyponatremia.
   D. Oxcarbazepine does not form an epoxide intermediate in its metabolism.

10. When you see G.Z. 6 months later for a follow-up, she tells you she is about 6 weeks pregnant. She has had no seizures since starting oxcarbazepine. Which strategy is best for G.Z.?
   A. Discontinue her seizure medication immediately.
   B. Change her seizure medication to topiramate.
   C. Continue her seizure medication.
   D. Change her seizure medication to lamotrigine.

II. ISCHEMIC STROKE

A. Epidemiology
   1. Updated definitions
      a. CNS infarction: Brain, spinal cord, or retinal cell death attributable to ischemia, according to pathologic evidence, imaging, or other objective evidence of cerebral, spinal cord, or retinal focal ischemic injury in a defined vascular distribution, *or* clinical evidence of cerebral, spinal cord, or retinal focal ischemic injury, given symptoms persisting for 24 hours or more or until death, and other etiologies excluded
      b. Ischemic stroke: An episode of neurologic dysfunction caused by focal cerebral, spinal, or retinal infarction
   2. Third or fourth most common cause of death in all developed countries
   3. More than 795,000 cases per year in the United States (128,842 deaths)
   4. Most common cause of adult disability

5. Risk factors
    a. Nonmodifiable
        i. Age: Stroke risk doubles each decade after 55 years.
        ii. Race: Stroke risk for American Indian populations is greater than for African American populations, whose risk is greater than for White populations.
        iii. Sex: Risks are greater for men than for women; however, about one-half of strokes occur in women.
        iv. Low birth weight: Odds of stroke for those with birth weights less than 2500 g are twice has high as the odds for those weighing more than 4000 g.
        v. Family history: Parental history increases risk; some coagulopathies (e.g., protein C and S deficiencies, factor V Leiden mutations) are inherited.
        vi. Systemic lupus erythematosus
    b. Somewhat modifiable: Diabetes increases risk 1.8–6 times; risk reduction has not been shown for glycemic control.
    c. Modifiable
        i. Hypertension increases risk 1.4–8 times; 32% risk reduction with control
        ii. Smoking increases risk 1.9 times; 50% risk reduction in 1 year, baseline risk of stroke at 5 years with smoking cessation; exposure to environmental cigarette smoke also increases risk
        iii. Oral contraceptives with less than 50 mcg of estrogen double the risk of stroke; those with more than 50 mcg of estrogen have a 4.5 times increased risk; risk increases with age; adding smoking to oral contraceptive use increases the risk of stroke 7.2 times; obesity and hypertension also increase the risk with oral contraceptives.
        iv. Postmenopausal hormone therapy increases risk 1.4 times.
        v. Atrial fibrillation increases risk 2.6–4.5 times; 68% risk reduction with warfarin; direct oral anticoagulants have risk reduction similar to warfarin
        vi. Coronary heart disease increases risk 1.55 times (women) to 1.73 times (men).
        vii. Asymptomatic carotid stenosis increases risk 2 times; about a 50% risk reduction with endarterectomy
        viii. Dyslipidemia: High TC increases risk 1.5 times; low HDL (less than 35 mg/dL) increases risk 2 times; 27%–32% risk reduction with statins in patients with coronary heart disease, hypertension, or diabetes. Twenty-five percent risk reduction with high-dose statins compared with low-dose statins
        ix. Obesity (especially abdominal body fat) increases risk 1.75–2.37 times; risk reduction with weight loss is unknown.
        x. Physical inactivity increases risk 2.7 times; risk reduction with increased activity is unknown.
        xi. Sickle cell disease increases risk 200–400 times; 91% risk reduction with transfusion therapy
        xii. Peripheral artery disease increases risk 3 times; impact of risk reduction strategies is unknown.
        xiii. Pregnancy increases risk by 2.4 times over nonpregnant women; the risk remains elevated for the first 6 weeks after delivery.
        xiv. Patent foramen ovale increases the risk of stroke in young patients (younger than 55 years).
        xv. Risk of stroke is increased 1.35 times in depressed people compared with nondepressed people.
    d. Less well documented: Alcohol use disorder (5 or more drinks a day), hyperhomocystinemia, drug use disorder (cocaine, amphetamines, and heroin), hypercoagulability, periodontal disease, inflammation and infection, sleep-disordered breathing (sleep apnea and snoring), metabolic syndrome, and migraine with aura

B. Primary Prevention
   1. Reduction in risk factors (e.g., control of hypertension, smoking cessation, control of diabetes, cholesterol reduction). Control of hypertension produces the greatest benefit in primary prevention of stroke.
   2. Patient education: Patients should be educated about stroke warning signs and instructed to seek emergency care if they have any of them. Warning signs: Sudden numbness or weakness of the face, arm, or leg, especially on one side of the body; sudden confusion; trouble speaking or understanding; sudden trouble seeing in one or both eyes; sudden trouble walking; dizziness, loss of balance or coordination; sudden, severe headache with no known cause
   3. Treatment of atrial fibrillation: Up to 70% of cases are inappropriately treated. (For a more detailed discussion, see the Anticoagulation chapter.)
      a. Dabigatran (Pradaxa): When oral anticoagulation is recommended and the patient's bleeding risk is high, current guidelines suggest dabigatran 150 mg twice daily over warfarin (target INR of 2.5). Dabigatran had similar rates of hemorrhage, but intracranial hemorrhage was less likely with dabigatran and GI hemorrhage was more likely.
      b. Rivaroxaban (Xarelto) was noninferior to warfarin therapy and had a similar risk of major bleeding. Rivaroxaban had a higher risk of GI bleeding, but a lower risk of intracranial hemorrhage and fatal bleeding, compared with warfarin therapy.
      c. Apixaban (Eliquis) is more effective than warfarin, with a lower risk of stroke and lower risk of bleeding and mortality.
      d. Edoxaban (Savaysa) is as effective as warfarin, with a lower risk of bleeding.
      e. Warfarin (Coumadin) is probably more effective than clopidogrel plus aspirin, but intracranial bleeding is more common.

C. Treatment of Acute Event
   1. Heparin
      a. Good data on outcomes are unavailable; not recommended for stroke treatment at therapeutic doses; increases risk of hemorrhagic transformation; heparin is often used for deep venous thrombosis prevention at a dose of 10,000–15,000 units/day administered subcutaneously
      b. Avoid in hemorrhagic stroke.
   2. Tenecteplase (TNKase)
      a. Recombinant tissue plasminogen activator (tPA)
      b. Not FDA approved for acute ischemic stroke treatment.
      c. Current guidelines only recommend alteplase for acute ischemic stroke treatment.
      d. Longer half-life than alteplase and resists inhibition from plasminogen activator inhibitor-1. These allow tenecteplase to be administered as a one-bolus dose.
      e. There has been growing evidence regarding the use of tenecteplase for acute ischemic stroke.
         i. Overall findings support similar safety and efficacy between alteplase and tenecteplase for the treatment of acute ischemic stroke.
         ii. Meta-analysis comparing alteplase and tenecteplase for the treatment of acute ischemic stroke found tenecteplase noninferior to alteplase (Stroke 2019;50:2156-62).
      f. In many practice settings, tenecteplase is used to treat acute ischemic stroke based on the growing amount of primary literature and ease of use, even without the FDA indication or updated guideline recommendation.
   3. Tissue plasminogen activator (Alteplase)
      a. Within 4½ hours of symptom onset
      b. 90-day outcomes significantly improve (decreased disability).
      c. Intracerebral hemorrhage increases but mortality does not.
      d. Dose 0.9 mg/kg intravenously (maximum is 90 mg), with 10% as a bolus and the remainder over 1 hour. The bolus should be administered within 60 minutes of hospital arrival.

e. Antiplatelet agents should be held for 24 hours after tissue plasminogen activator administration.
f. Exclusion criteria
    i. Intracranial bleeding (or history) or subarachnoid bleeding
    ii. Other active internal bleeding
    iii. Intracranial/spinal surgery, head trauma, stroke within 3 months
    iv. Major surgery or serious trauma within 2 weeks, if risk of bleeding outweighs the anticipated benefits of reduced stroke-related neurologic deficits
    v. GI hemorrhage within 3 weeks or structural GI malignancy
    vi. Blood pressure greater than 185/110 mm Hg. If medications are administered to lower blood pressure, blood pressure should be stabilized before beginning treatment and maintained below 180/105 mm Hg for at least the first 24 hours after treatment.
    vii. Glucose less than 50 mg/dL or greater than 400 mg/dL, unless subsequently normalized
    viii. Arterial puncture at a noncompressible site within 1 week
    ix. Intracranial intra-axial neoplasm, arteriovenous malformation, or giant unruptured and unsecured aneurysm
    x. INR greater than 1.7, activated PTT greater than 40 seconds, PT greater than 15 seconds, Plt less than 100,000 cells/m^3, patients who have received a dose of low-molecular-weight heparin within the previous 24 hours, or patients who have taken direct thrombin inhibitors or direct factor Xa inhibitors in the previous 48 hours
    xi. Infective endocarditis
    xii. Pregnancy, if the anticipated benefits of treating moderate to severe stroke do not outweigh the anticipated risks of uterine bleeding
    xiii. Individuals presenting in the 3- to 4½-hour window may benefit even if they are older than 80, take warfarin, have a history of diabetes with previous stroke, or have severe stroke symptoms (NIHSS [National Institutes of Health Stroke Scale] score greater than 25).

4. In patients with minor strokes or transient ischemic attack (TIA), DAPT with aspirin and clopidogrel should be initiated immediately and continued for 21 days.
5. A clot retriever within 24 hours may be useful in selected patients with or without prior tissue plasminogen activator.

D. Secondary Prevention
1. Reduction in all modifiable risk factors (specific changes in the text that follows according to Stroke 2021;52:e364-e467)
    a. Hypertension: Goal less than 130/less than 80 mm Hg. With lacunar stroke, may target less than 130 mm Hg systolic
    b. Hyperlipidemia: High-intensity statin therapy should be initiated or continued as first-line therapy in women and men younger than 75 who have had stroke or TIA.
2. Carotid endarterectomy if 70%–99% stenosis. For 50%–69% stenosis, the carotid endarterectomy recommendation depends on age, sex, and comorbidities; use aspirin 50–100 mg/day and statin therapy before and after the procedure.
3. Carotid angioplasty and stenting may be an alternative to carotid endarterectomy in some patients, particularly younger patients.
4. Antiplatelet therapy: DAPT with aspirin and clopidogrel should be initiated within 24 hours of a minor stroke or TIA and continued for 21 days. After a major stroke (e.g., intracranial atherosclerosis, severe stenosis), DAPT with aspirin and clopidogrel should be initiated and continued for 90 days. After these time intervals, therapy should be transitioned to single antiplatelet therapy and continued indefinitely. Each agent has shown efficacy in reducing secondary stroke risk. Guidelines differ slightly on their recommendations. The American Stroke Association suggests that aspirin, aspirin/extended-release dipyridamole, and clopidogrel are all options for ongoing prophylaxis.

a. Aspirin
   i. Dose: 50–100 mg/day
   ii. If the patient has an additional stroke while taking aspirin, no evidence suggests increasing the aspirin dose will provide additional benefit.
b. Aspirin/dipyridamole (Aggrenox)
   i. Capsule contains dipyridamole extended-release pellets (200 mg) and aspirin tablet (25 mg).
   ii. Dose: 1 capsule orally twice daily
   iii. Most common adverse effects: Headache, nausea, and dyspepsia; can increase liver enzymes
c. Clopidogrel (Plavix)
   i. Inhibits adenosine diphosphate–induced platelet aggregation
   ii. Dose: 75 mg/day orally
   iii. Very low incidence of neutropenia (0.04% severe)
   iv. Rarely, thrombotic thrombocytopenic purpura has been reported.
   v. Partly metabolized by CYP2C19; interactions may occur with inhibitors of CYP2C19, notably proton pump inhibitors, or with genetic polymorphisms of this enzyme. The FDA has issued an alert on this topic (www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm190787.htm).
d. Cilostazol (Pletal)
   i. Inhibits cyclic adenosine monophosphate phosphodiesterase type 3–induced platelet aggregation
   ii. Dose: 100 mg orally twice daily on an empty stomach
   iii. Metabolized extensively by CYP3A4 and CYP2C19
   iv. Adverse effects: Headache, palpitation, diarrhea, and dizziness; rarely, thrombocytopenia or agranulocytosis
   v. Contraindicated in patients with congestive heart failure
   vi. Monitoring: CBC with differential every 2 weeks for 3 months; periodically thereafter. Thus, used infrequently

5. Anticoagulation: Warfarin (Athrombin-K, Coumadin, Jantoven, Panwarfin) or direct oral anticoagulants (dabigatran, rivaroxaban, apixaban, edoxaban)
   a. Prevention of second ischemic event, if patient has atrial fibrillation (warfarin or direct oral anticoagulants), rheumatic mitral valve disease (warfarin), mechanical prosthetic heart valves (warfarin), bioprosthetic heart valves (warfarin), or left ventricular mural thrombus formation (warfarin)
   b. Target INR: 2–3 for nonvalvular atrial fibrillation; 2.5–3.5 for mechanical prosthetic heart valves

Patient Cases

Questions 11–14 pertain to the following case.

L.R. is a 78-year-old woman who presents to the ED for symptoms of right-sided paralysis. She states these symptoms began about 6 hours ago and have not improved. She also has hypertension, breast cancer, diabetes, minimal cognitive impairment, and osteoarthritis. L.R. is diagnosed with a minor stroke by the neurology team.

11. Which is the most accurate list of L.R.'s risk factors for stroke?
    A. Breast cancer, age, osteoarthritis.
    B. Sex, diabetes, osteoarthritis.
    C. Minimal cognitive impairment, diabetes, age, sex.
    D. Age, diabetes, hypertension.

Patient Cases (*Cont'd*)

12. Which best describes whether L.R. is a candidate for tissue plasminogen activator (Alteplase) for the treatment of stroke?
    A. Yes.
    B. No, because of advanced age.
    C. No, her stroke symptoms began too long ago.
    D. No, her breast cancer is a contraindication for tissue plasminogen activator.

13. L.R. previously took no home medications. Which is the best treatment at this time for her?
    A. Metformin and aspirin.
    B. Celecoxib and clopidogrel.
    C. Aspirin and clopidogrel.
    D. Warfarin.

14. L.R. presents to her community pharmacy to pick up her medication refills (lisinopril, aspirin, clopidogrel, atorvastatin) 2 months after her discharge from the hospital. Which best assesses her dual antiplatelet therapy (DAPT)?
    A. Appropriate, continue for 90 days after stroke.
    B. Appropriate, continue as chronic therapy.
    C. Inappropriate, single antiplatelet therapy should be initiated for 90 days.
    D. Inappropriate, single antiplatelet therapy should be initiated indefinitely.

15. L.S. is a 42-year-old woman with a medical history of hypertension, type 2 diabetes, renal failure, and mitral valve replacement. She presents to the anticoagulation clinic for her initial visit. Which best reflects her target INR?
    A. 1.5.
    B. 2.0.
    C. 2.5.
    D. 3.0.

III. PARKINSON DISEASE

A. Epidemiology
   1. Prevalence is 1 million in the United States.
   2. Onset is usually at 40–70 years of age, with peak onset in the sixth decade.
   3. Slightly more common in men
   4. Observed in all countries, ethnic groups, and socioeconomic classes

B. Signs and Symptoms
   1. Cardinal signs
      a. Akinesia or hypokinesia
      b. Rigidity
      c. Tremor
      d. Posture or gait abnormalities

2. Secondary signs
    a. Cognitive dysfunction
    b. Autonomic dysfunction
    c. Speech disturbances
    d. Micrographia
    e. Masked facies

C. Treatment
1. General treatment principles
    a. No treatment has unequivocally been shown to prevent the progression of Parkinson disease; therefore, treatment is based on symptoms.
    b. In patients who need the initiation of dopaminergic treatment, either levodopa or a dopamine agonist may be used. Choice depends on the relative impact of improving motor disability (better with levodopa) compared with the lessening of motor complications (better with dopamine agonists) for each patient.
    c. Treatment may be initiated with rasagiline as well, but the effects are not robust.
    d. Treatment with several different classes of medications simultaneously is common.
    e. General framework for Parkinson symptoms and treatments
        i. Tremor
            (a) Carbidopa/levodopa
            (b) Dopamine agonists
            (c) Anticholinergics
        ii. Bradykinesia
            (a) Carbidopa/levodopa
            (b) Dopamine agonists
        iii. Rigidity
            (a) Carbidopa/levodopa
            (b) Dopamine agonists
        iv. Gait disturbances: No treatment at this time
2. Medications
    a. Monoamine oxidase type B (MAO-B) inhibitors
        i. Inhibition of MAO-B allows more dopamine to be available in the brain, thus helping with Parkinson disease movement symptoms.
        ii. Selegiline (Eldepryl, Zelapar)
            (a) Loses selectivity for MAO-B at doses greater than 10 mg/day
            (b) Contraindicated with meperidine because of serotonin syndrome risk
            (c) Do not administer with tramadol, methadone, dextromethorphan, sympathomimetics, fluoxetine, or fluvoxamine because of serotonin syndrome risk.
            (d) Dose: 5 mg orally twice daily (tablets; usually morning and noon); 1.25–2.5 mg/day (orally disintegrating tablets)
            (e) Adverse effects: Nausea, hallucinations, orthostatic hypotension, insomnia (metabolized to amphetamine)
            (f) Dosage forms: Tablets, orally dissolving tablets, and patches. The patches are FDA indicated for depression; they should not usually be used for Parkinson disease.
        iii. Rasagiline (Azilect)
            (a) Selectivity for MAO-B has not been definitively established.
                (1) Contraindicated with meperidine because of serotonin syndrome risk
                (2) Do not administer with tramadol, methadone, dextromethorphan, sympathomimetics, fluoxetine, or fluvoxamine because of serotonin syndrome risk.

(3) Ciprofloxacin can double the concentration of rasagiline (through CYP1A2 inhibition).
(b) Dose: 0.5–1 mg/day orally
iv. Safinamide (Xadago)
(a) Highly selective MAO-B inhibitor
(b) Dose: 50–100 mg daily
(c) Reduce dose in hepatic failure (Child-Pugh class C).
(d) Adverse effects and drug interactions similar to other MAO-B inhibitors

b. Istradefylline (Nourianz)
i. Adenosine receptor antagonist
ii. Adjunct to carbidopa/levodopa
iii. Treats off-episodes
iv. Dose: 20 mg daily; may increase to maximum of 40 mg daily
v. Those who smoke tobacco (20 or more cigarettes/day) have decreased systemic exposure and thus require a higher dose of istradefylline (40 mg once daily).
vi. Adverse effects: Dyskinesia, dizziness, constipation, nausea, hallucinations, insomnia
vii. Drug interactions: CYP3A4 substrate; avoid use with CYP3A4 inducers; maximum dose is 20 mg daily with CYP3A4 inhibitors

c. Levodopa inhalation powder (Inbrija)
i. Treats off-episodes
ii. Dose: 2 capsules (84 mg) inhaled as needed, up to five times daily
iii. Adverse effects: Cough, nausea, discolored sputum

d. Carbidopa
i. Combined in fixed ratios with levodopa
ii. Prevents some of the peripheral conversion of levodopa to dopamine by inhibiting peripheral dopamine decarboxylase; therefore, levodopa is available to cross the blood-brain barrier
iii. 75 mg/day is usually needed to inhibit peripheral decarboxylase activity.

e. Carbidopa/levodopa (Parcopa, Sinemet, Duopa, Rytary)
i. Pharmacokinetic considerations
(a) High-protein diets and iron supplements decrease absorption.
(b) Immediate-release half-life 60–90 minutes
(c) Orally disintegrating tablet available; not absorbed sublingually
(d) Slow-release considerations: Fewer daily doses; less plasma fluctuations; delay to effect; cannot crush; can divide. No measurable effect on "freezing." Freezing is typically described as the sudden inability to move for several seconds to minutes. Freezing can also affect speech or repetitive fine-motor skills, but usually only affects certain parts of the body. In an off-episode/period, the patient can not move at all.
ii. Acute adverse effects: Nausea and vomiting, orthostatic hypotension, cardiac arrhythmias, confusion, agitation, hallucinations, peak-dose dyskinesia
iii. Long-term adverse effects: Wearing-off and on-off phenomena, involuntary movements (dyskinesias)
(a) Wearing-off phenomenon is the return of Parkinson disease symptoms before the next dose. Treatment of wearing-off includes adding a dopamine agonist, adding a MAO-B inhibitor, adding a catechol-*O*-methyltransferase (COMT) inhibitor, or increasing the frequency or dose of levodopa.
(b) On-off phenomenon is a profound, unpredictable return of Parkinson disease symptoms without respect to the dosing interval. Treatment of on-off includes adding entacapone, rasagiline, pramipexole, ropinirole, apomorphine, or selegiline or redistributing dietary protein.

(c) Dyskinesias are drug-induced involuntary movements, including chorea and dystonia. Treatment of dyskinesias includes decreasing the levodopa dose or adding amantadine as an antidyskinetic drug.

iv. Therapy initiation
   (a) Standard formulation: 25 mg/100 mg 1 tablet orally three times daily; also available as orally disintegrating tablet
   (b) Controlled-release formulation: 1 tablet orally two or three times daily
   (c) Titration is always necessary.
   (d) A combination of formulations may be needed (e.g., ½ tablet of Sinemet 25 mg/100 mg on awakening and 1 tablet of Sinemet CR 25/100 three times daily).

v. Levodopa may improve disability and mortality.

vi. Greatest benefit for rigidity and bradykinesia, less benefit for tremor and postural instability

f. Direct dopamine agonists

i. Drugs: Apomorphine (Apokyn), bromocriptine (Parlodel), pramipexole (Mirapex), ropinirole (Requip), rotigotine (Neupro)

ii. Bromocriptine is an ergot-derived product: Very rarely, adverse effects such as retroperitoneal, pleuropulmonary, or cardiac fibrosis have been attributed to it; regular ECG monitoring is recommended.

iii. Rotigotine is a transdermal system. With the initial formulation, problems occurred with crystallization of the medication. The product was withdrawn from the market and has since been reformulated. Rotigotine is currently available.

iv. Dosing: Always titrate to final dose (Table 6).

Table 6. Usual Dosage Range for Dopamine Agonists

Agent	Usual Dosage Range (mg/day)
Bromocriptine	5–40
Pramipexole	1.5–4.5
Ropinirole	0.75–24
Rotigotine	6–8

v. Adverse effects: Nausea, vomiting, postural hypotension, hallucinations, impulsive behaviors (e.g., hypersexuality, gambling, shopping, eating), falling asleep during activities of daily living

vi. Pramipexole and ropinirole also have FDA indications for restless legs syndrome.

vii. Ropinirole and pramipexole are available as extended-release formulations.

viii. Apomorphine: Short-acting dopamine receptor agonist
   (a) Indication: Acute, intermittent treatment of off-episodes associated with advanced Parkinson disease
   (b) Contraindications: Use with 5-hydroxytryptamine-3 antagonists (ondansetron, granisetron, dolasetron, palonosetron, and alosetron) causes profound hypotension, sulfite sensitivity, or allergy.
   (c) Pharmacokinetics: When administered orally, poorly bioavailable and extensive first-pass metabolism; used as subcutaneous injection in a pen self-injector
   (d) Adverse effects
      (1) Severe nausea and vomiting
         (A) Treat with trimethobenzamide 300 mg three times daily for 3 days before initiating treatment and for at least 6 weeks during treatment.

(B) About 50% of patients can discontinue trimethobenzamide after 2 months.
(C) Thirty-one percent of patients had nausea and 11% had vomiting with trimethobenzamide.
(2) Hypotension
(3) Hallucinations
(4) Injection site reactions
(5) Dyskinesias
(e) Dosing
(1) Must be titrated in a setting where blood pressure can be monitored
(2) In the "off" state, the patient should be administered a 0.2-mL (2 mg) test dose.
(3) Supine and standing blood pressure taken before dose; 20, 40, and 60 minutes after dose
(4) If tolerated, begin with a 0.2-mL dose as needed; increase by 0.1 mL, if necessary.
(5) Doses greater than 0.6 mL, more than five times daily, or greater than 20 mg/day have limited experience.
(6) If first dose is ineffective, do not re-dose.
(7) If patients do not dose for more than 1 week, reinitiate at a 0.2-mL dose.

g. Anticholinergics
i. Drugs: Trihexyphenidyl (Artane), benztropine (Cogentin)
ii. Useful only for tremor
iii. Initial dosing
(a) Trihexyphenidyl 0.5 mg 1 tablet orally twice daily
(b) Benztropine 0.5 mg 1 tablet orally twice daily
iv. Adverse effects: Dry mouth, urinary retention, dry eyes, constipation, confusion

h. Amantadine (Symmetrel)
i. Has symptomatic benefits and may reduce dyskinesias caused by levodopa or dopamine agonists
ii. Dosing: 100 mg 1 tablet orally two or three times daily; caution in renal dysfunction
iii. Adverse effects: Dizziness, insomnia, anxiety, livedo reticularis, nausea, nightmares

i. COMT inhibitors
i. Prevent breakdown of dopamine, more levodopa available to cross blood-brain barrier
ii. Tolcapone (Tasmar): Severely restricted because of hepatotoxicity; must sign consent form
iii. Entacapone (Comtan)
(a) Increased AUC, increased half-life; no change in Cmax or Tmax of levodopa
(b) Dosing: 1 tablet with each carbidopa/levodopa dose; maximum of eight times daily; one dosage form (Stalevo) includes carbidopa, levodopa, and entacapone 200 mg
(c) Must use with carbidopa/levodopa
(d) Adverse effects: Dyskinesias, nausea, diarrhea (may be delayed for up to 2 weeks after initiation or dose increase), urine discoloration (orange), hallucinations or vivid dreams
iv. Opicapone (Ongentys)
(a) Dosing: 50 mg daily at bedtime
(b) Take doses 1 hour before or after eating.
(c) Reduce dose by 50% with moderate hepatic failure. Avoid use in severe hepatic failure.

3. Surgery: Several types of surgery are done for Parkinson disease.
a. Thalamotomy: Ablation of portions of the thalamus to control tremor
b. Pallidotomy: Ablation of structures in the globus pallidus for the treatment of Parkinson disease
c. Fetal transplants: Transplantation of dopaminergic tissue into the striatum; considered experimental
d. Trophic factors: Glial-derived nerve growth factor and neurturin have been delivered directly to the striatum or substantia nigra; considered experimental

e. Deep brain stimulation
    i. Most common surgery for Parkinson disease
    ii. Thought to stimulate areas of the basal ganglia to reversibly block the neuronal activity in the area
    iii. Patient selection focuses on patients with:
        (a) Motor fluctuations or dyskinesias that are inadequately controlled with optimized medical therapy
        (b) Medication-refractory tremor
        (c) Intolerance of medical therapy
        (d) Some centers will not do the surgery in patients older than 70.
    iv. Two areas are targeted.
        (a) Globus pallidum
            (1) Reduces off-time
            (2) Reduces dyskinesias
            (3) Thought to have fewer cognitive adverse effects than subthalamic nucleus stimulation
        (b) Subthalamic nucleus
            (1) Reduces off-time
            (2) Reduces dyskinesias
            (3) Thought to be more effective than globus pallidum stimulation

4. Special situations
    a. Hallucinations or psychosis may be caused by either Parkinson disease or treatment.
        i. Discontinue or reduce Parkinson disease medications as tolerated. Reduce antiparkinson medications to minimum the therapeutic dose or discontinue. Start with anticholinergics; then use MAO-B inhibitors, amantadine, dopamine agonists, COMT inhibitors; finally, use carbidopa/levodopa
        ii. Pimavanserin (Nuplazid): FDA approved for Parkinson disease psychotic disorder
        iii. If an antipsychotic is needed, use quetiapine or clozapine as the first choice.
        iv. Avoid typical antipsychotics, risperidone, and olanzapine because they may worsen motor features associated with Parkinson disease.
    b. Cognitive disorders
        i. Discontinue or reduce Parkinson disease medications as tolerated.
        ii. Rivastigmine (Exelon) has an FDA indication for treatment; other cholinesterase inhibitors may have efficacy.
        iii. Memantine lacks data to recommend it for cognitive disorders associated with Parkinson disease.
    c. Sleep disorders, depression, agitation, anxiety, constipation, orthostatic hypotension, seborrhea, blepharitis, and restless legs syndrome can occur in Parkinson disease; treat as usual.

Patient Cases

Questions 16 and 17 pertain to the following case.

L.T. takes carbidopa/levodopa 25 mg/100 mg orally four times daily and trihexyphenidyl 2 mg orally three times daily for Parkinson disease. L.T.'s wife reports that his movements are very slow and that he is having trouble walking.

16. Given these symptoms, which change seems most reasonable?
    A. Increase carbidopa/levodopa, discontinue trihexyphenidyl.
    B. Continue carbidopa/levodopa, increase trihexyphenidyl.
    C. Decrease carbidopa/levodopa, continue trihexyphenidyl.
    D. Decrease carbidopa/levodopa, increase trihexyphenidyl.

Patient Cases (*Cont'd*)

17. Six months later, L.T. returns to the clinic concerned that his carbidopa/levodopa dose is wearing off before his next dose is due, because his tremor and slow movements are worse before the next dose of carbidopa/levodopa. Which recommendation is best?
    A. Increase the carbidopa/levodopa dose.
    B. Decrease the carbidopa/levodopa dose.
    C. Increase the dosing interval.
    D. Decrease the dosing interval.

18. P.J. is a 57-year-old man with an 8-year history of Parkinson disease. His current medications include carbidopa/levodopa 50 mg/200 mg orally four times daily, entacapone 200 mg orally four times daily, and amantadine 100 mg three times daily. He presents to the clinic with concerns of reddish orange urine. He fears he has blood in his urine. Which most likely caused this condition?
    A. Carbidopa/levodopa.
    B. Entacapone.
    C. Amantadine.
    D. Hemorrhagic cystitis.

19. L.L. is a 47-year-old man with Parkinson disease. He takes carbidopa/levodopa 50 mg/200 mg orally four times daily. His wife states that he cannot sit still during the day. He is constantly moving, and she fears his disease is worsening. Which is the best therapy for L.L.?
    A. Add ropinirole.
    B. Add selegiline.
    C. Increase the carbidopa/levodopa dose.
    D. Decrease the carbidopa/levodopa dose.

20. C.A. is a 70-year-old man with tremors in his right hand that have progressively worsened for the past 6 months. He has difficulty walking. He also has backaches and no longer plays golf. In addition, he is losing his sense of taste. His wife notes that he is moving more slowly and that his handwriting has deteriorated. He is diagnosed with Parkinson disease. Which is the best treatment for C.A.?
    A. Trihexyphenidyl.
    B. Apomorphine.
    C. Carbidopa/levodopa.
    D. Istradefylline.

IV. HEADACHE

A. Definitions
    1. Migraine with aura: At least two attacks with at least three of the following: One or more fully reversible aura symptoms, at least one aura symptom for more than 4 minutes, or two or more symptoms occurring in succession; no single aura symptom lasts more than 60 minutes; headache follows aura within 60 minutes

2. Migraine without aura: At least five attacks of headache lasting 4–72 hours with at least two of the following: Unilateral location, pulsating quality, intensity moderate or severe, aggravation by walking stairs or similar routine physical activity. During headache, at least one of the following: Nausea or vomiting, photophobia, phonophobia
3. Status migrainosus: Attack of migraine, with headache phase lasting more than 72 hours despite treatment. Headache-free intervals of less than 4 hours (sleep not included) may occur.
4. Tension: At least 10 previous headaches, each lasting from 30 minutes to 7 days, with at least two of the following: Pressing or tightening (nonpulsating) quality, intensity mild to moderate, bilateral location, no aggravation with physical activity
5. Cluster: Several episodes, short-lived but severe, of unilateral, orbital, supraorbital, or temporal pain. At least one of the following must occur: conjunctival injection, lacrimation, nasal congestion, rhinorrhea, facial sweating, miosis, ptosis, or eyelid edema.
6. Medication overuse headache: If patients use analgesics often (usually defined as more than three times weekly), they may develop medication overuse headache. Patients with this condition usually present with a chronic daily headache, for which they take simple or narcotic analgesics. Treatment consists of the withdrawal of all analgesics (but not prophylactic medications).

B. Epidemiology
   1. Migraine: 15%–17% of women, 5% of men
   2. Tension: 88% of women, 69% of men
   3. Cluster: 0.01%–1.5% of population; ratio of men to women is 6:1

C. Treatment
   1. Migraine
      a. Prophylaxis should be considered if any of the following criteria are met: Migraines are recurrent and interfere with daily routine, migraines are frequent, patient has inefficacy with or inability to use acute therapy, patient prefers prophylaxis as therapy, cost of acute medications is problematic, adverse effects or contraindications with acute therapies occur, or migraine presentation is uncommon
         i. General principles
            (a) Use lowest effective dose.
            (b) Give adequate trial (2–3 months).
            (c) If the patient has a coexisting condition, consider prophylaxis choice (e.g., β-blockers are contraindicated in patients with asthma but beneficial in patients with hypertension).
         ii. Medications with established efficacy for migraine prevention
            (a) Atogepant
            (b) Candesartan
            (c) Eptinezumab
            (d) Erenumab-aooe
            (e) Fremanezumab-vfrm
            (f) Frovatriptan (for menstrually associated migraine, short-term prophylaxis only)
            (g) Galcanezumab-gnlm
            (h) Metoprolol
            (i) OnabotulinumtoxinA
            (j) Propranolol
            (k) Rimegepant
            (l) Timolol
            (m) Topiramate
            (n) Valproate

iii. Medications with probable efficacy
  (a) Amitriptyline
  (b) Atenolol
  (c) Ibuprofen
  (d) Ketoprofen
  (e) Lisinopril
  (f) Magnesium (recommend magnesium citrate for better absorption)
  (g) Memantine
  (h) Nadolol
  (i) Naproxen/naproxen sodium
  (j) Naratriptan (for menstrually associated migraine, short-term prophylaxis only)
  (k) Venlafaxine
  (l) Zolmitriptan (for menstrually associated migraine, short-term prophylaxis only)

iv. Calcitonin gene-related peptide antagonists are highly effective in refractory migraine headache prophylaxis.
  (a) Parenteral options:
    (1) Erenumab-aooe (Aimovig): Dose: 70–140 mg subcutaneously monthly
    (2) Fremanezumab-vfrm (Ajovy): Dose: 225 mg subcutaneously monthly or 675 mg subcutaneously quarterly (administered as three separate injections)
    (3) Galcanezumab-gnlm (Emgality): Dose: Two consecutive doses of 120 mg subcutaneously for a total of a 240-mg loading dose, followed by doses of 120 mg subcutaneously monthly
    (4) Eptinezumab (Vyepti): Dose: 100 mg intravenously every 3 months. Adverse effects with parenteral calcitonin gene-related peptide antagonists: Injection site reactions; severe constipation (erenumab only)
  (b) Oral options:
    (1) Atogepant (Qulipta): Dose 10 mg, 30 mg, or 60 mg orally once daily
    (2) Rimegepant (Nurtec ODT): Dose 75 mg orally every other day

b. Acute treatment
  i. Triptans (Table 7)
    (a) Sumatriptan and zolmitriptan have nonoral administration routes (subcutaneous [sumatriptan], intranasal [sumatriptan and zolmitriptan]) that should be considered for patients with nausea or vomiting.
    (b) Orally disintegrating tablets are available for zolmitriptan and rizatriptan if patients do not have access to water; however, they do not work faster than oral tablets and are not absorbed sublingually.
    (c) All are contraindicated in patients with or at risk of coronary artery disease, stroke, uncontrolled hypertension, peripheral vascular disease, ischemic bowel disease, and pregnancy (sumatriptan and rizatriptan may be considered in pregnancy); they should not be used in patients with hemiplegic or basilar migraines.
    (d) Drug interactions: Contraindicated within 2 weeks of MAO inhibitors; do not use within 24 hours of ergotamines; caution with other serotonin-active medications. Propranolol increases serum concentrations of rizatriptan; thus, a maximum 5-mg dose should be used with propranolol, and the dose should not exceed 15 mg/day.
  ii. Ergots
    (a) Dihydroergotamine has nonoral administration routes (subcutaneous, intravenous, and intranasal) that can be considered for patients with nausea or vomiting.

(b) All are contraindicated in patients with, or at risk of, coronary artery disease, stroke, uncontrolled hypertension, peripheral vascular disease, ischemic bowel disease, and pregnancy; they should not be used in patients with hemiplegic or basilar migraines.

iii. Lasmiditan (Reyvow)
(a) Mechanism of action: Serotonin-1F receptor agonist
(b) Dose: 50–200 mg at start of headache, may only take one dose per 24 hours
(c) Adverse effects: Dizziness, fatigue, paresthesia, sedation
(d) Avoid driving for at least 8 hours after dose.
(e) Controlled substance: Schedule V

iv. Ubrogepant (Ubrelvy)
(a) Mechanism of action: Calcitonin gene-related peptide receptor antagonist
(b) Dose: 50–100 mg at start of headache, may repeat once after 2 hours
(c) Adverse effects: Nausea, somnolence
(d) Drug interactions: Avoid use with strong CYP3A4 inducers. Dose adjustments may be needed with moderate or weak CYP3A4 inhibitors or inducers and/or P-glycoprotein (P-gp) inhibitors.

v. Rimegepant (Nurtec)
(a) Mechanism of action: Calcitonin gene-related peptide receptor antagonist
(b) Dose: 75 mg at start of headache; should not exceed 15 doses in 30 days
(c) Adverse effects: Nausea
(d) Drug interactions: Avoid use with strong CYP3A4 inhibitors, strong or moderate inducers, or P-gp and breast cancer resistance protein (BCRP) inhibitors; with moderate CYP3A4 inhibitors, avoid a second dose within 48 hours.

vi. Zavegepant (Zavzpret)
(a) Mechanism of action: Calcitonin gene-related peptide (CGRP) receptor antagonist
(b) Dose: 10 mg single spray in 1 nostril as needed; not to exceed 10 mg/24 hours. Do not test spray, prime, or press plunger before use.
(c) Adverse effects: Taste disorder, nausea, nasal discomfort, vomiting
(d) Drug interactions: Intranasal decongestants may decrease zavegepant serum concentrations. Avoid concurrent administration. If combined use is unavoidable, administer inhaled decongestants greater than 1 hour after zavegepant.

vii. NSAIDs: Usually effective for only mild to moderate headache pain

viii. Opioids: Butorphanol has a nonoral administration route (intranasal) that may be considered for patients with nausea or vomiting.

ix. Isometheptene combination products: Conflicting evidence about efficacy

x. Antiemetics: Prochlorperazine, metoclopramide, and chlorpromazine are most commonly used; they may have independent antimigraine action; all are available in nonoral forms. Often used in combination with acute migraine treatments to reduce nausea and vomiting

2. Status migrainosus treatments
a. Corticosteroids: Either intravenous or oral dosing
b. Dihydroergotamine: Intravenous dosing
c. Sodium valproate: Intravenous loading
d. NSAIDs: Ketorolac intravenous dosing

3. Tension
a. Prophylaxis
i. Tricyclic antidepressants
ii. Botulinum toxin

b. Acute treatment
    i. Simple analgesics (alone or with caffeine) and NSAIDs: Acetaminophen, aspirin, ibuprofen, naproxen, ketoprofen, and ketorolac
    ii. Used for mild to moderate tension-type headache
    iii. Do not use more than 2 days/week to prevent the development of chronic tension-type headache.
    iv. Failure of OTC agents warrants prescription therapy or analgesics with caffeine with:
        (a) High-dose NSAIDs, combinations with aspirin or acetaminophen with butalbital
        (b) Acetaminophen 250 mg/aspirin 250 mg/caffeine 65 mg
        (c) Acetaminophen 500 mg/caffeine 65 mg
    v. No evidence to support muscle relaxant use

4. Cluster
    a. Prophylaxis
        i. Verapamil
        ii. Melatonin
        iii. Suboccipital injection of betamethasone
        iv. Lithium: May be efficacious at serum concentrations as low as 0.3 mmol/L
        v. Warfarin
        vi. Galcanezumab-gnlm (Emgality): Two consecutive doses of 120 mg subcutaneously for a total of a 240-mg loading dose, followed by doses of 120 mg subcutaneously monthly
        vii. Corticosteroids
            (a) Consider in patients for whom all other preventive agents for cluster headache have failed.
            (b) Prednisone 40–60 mg/day, tapered over 3 weeks
            (c) Relief in 1 or 2 days
    b. Acute treatment
        i. Oxygen: 100% oxygen at 6–12 L/minute relieves pain in 50%–85% of patients.
        ii. Subcutaneous and intranasal routes are safe and effective.
            (a) Sumatriptan is available as subcutaneous and intranasal routes.
            (b) Zolmitriptan is available as intranasal route.
        iii. Subcutaneous route is the most effective.
        iv. Intranasal route is less effective but is better tolerated.
        v. Oral route has limited use because of relatively slow onset of action.
        vi. Intranasal lidocaine: 20–60 mg as a nasal drop or spray (must be compounded)
        vii. Octreotide and 10% cocaine have been used with some effect.
        viii. Dihydroergotamine intravenously/intramuscularly/subcutaneously: 1 mg as a single dose; maximum 2 mg/day and 6 mg/week

Table 7. Selected Agents for Acute Treatment of Migraine Headache

	Dosage Forms	Tmax	Half-Life (hr)	Dose	Maximal Dose/ 24 Hr (mg)
Triptans					
Almotriptan (Axert)	Tablets 6.25 mg, 12.5 mg	1–3 hr	2–4	1 tablet, may repeat in 2 hr	25
Eletriptan (Relpax)	Tablets 20 mg, 40 mg	1 hr	4–5	1 tablet, may repeat in 2 hr	80
Frovatriptan (Frova)	Tablets 2.5 mg	2–4 hr	26	1 tablet, may repeat in 2 hr	7.5
Naratriptan (Amerge)	Tablets 1 mg, 2.5 mg	2–3 hr	6	1 tablet, may repeat in 4 hr	5
Rizatriptan (Maxalt)	Tablets 5 mg, 10 mg	1–1.5 hr	1.8	1 tablet, may repeat in 2 hr	30
	Orally disintegrating tablets 5 mg, 10 mg	1.6–2.5 hr	1.8	1 tablet, may repeat in 2 hr	30
Sumatriptan (Alsuma, Imitrex, Sumavel, Zecuity)	SC injection 4 mg, 6 mg	12 min	1.9	1 injection, may repeat in 1 hr	12
	Intranasal 5 mg, 20 mg	30 min	2	1 spray in one nostril, may repeat in 2 hr	40
	Tablets 25 mg, 50 mg, 100 mg	2 hr	2.5	1 tablet, may repeat in 2 hr	200
Zolmitriptan (Zomig)	Tablets 2.5 mg, 5 mg	1.5 hr	3.75	1 tablet, may repeat in 2 hr	10
	Orally disintegrating tablets 2.5 mg, 5 mg	3 hr	3.75	1 tablet, may repeat in 2 hr	10
	Intranasal 2.5 mg, 5 mg	3 hr	3	1 spray in one nostril, may repeat in 2 hr	10
Triptan/NSAID combination					
Sumatriptan/naproxen sodium (Treximet)	Tablets 85 mg/500 mg	1 hr/5 hr	2/19	1 tablet, may repeat in 2 hr	170/1000
Calcitonin gene-related peptide antagonist (CGRP)					
Rimegepant (Nurtec ODT)	Orally disintegrating tablets 75 mg	1.5 hr	11	1 tablet, may be taken in 24 hr	75
Ubrogepant (Ubrelvy)	Tablets 50 mg, 100 mg	1.5 hr	5–7	1 tablet, may repeat in 2 hr	200
Zavegepant (Zavzpret)	Nasal spray 10mg/ actuation	30 min	6.55	1 spray, in one nostril as a single dose (10 mg)	10 mg (1 spray)
Serotonin-1F receptor agonist					
Lasmiditan (Reyvow)	Tablets 50 mg, 100 mg	1.8 hr	5.7	1 tablet, may be taken in 24 hr	One dose in 24 hr
Ergots					
Ergotamine tartrate (Ergomar)	Sublingual tablets 2 mg	2 hr	2	1 tablet under tongue, may repeat in ≥ 30 min	6
Dihydroergotamine (DHE 45; Migranal)	Intranasal 4-mg ampules	0.9 hr	10	1 spray (0.5 mg) in each nostril, repeat in 15 min	3
	IV/IM/SC 1 mg/mL 1-mLvials	SC 15–45 min	9	1 mg IV/IM, may repeat in 1 hr 1 mg SC, may repeat ≥ 2 hr	2 mg IV; 3 mg IM/SC

IM = intramuscular(ly); IV = intravenous(ly); SC = subcutaneous(ly).

Patient Cases

21. M.R., a 29-year-old woman, has throbbing right-sided headaches. She experiences nausea, phonophobia, and photophobia with these headaches but no aura. She usually has headaches twice a month. She has hypertension and morbid obesity. She takes hydrochlorothiazide 25 mg/day orally for hypertension, which is the only medication she is taking. Which medication is best for prophylaxis of her headaches?
    A. Propranolol.
    B. Indomethacin.
    C. Topiramate.
    D. Sumatriptan.

22. S.R. is a 54-year-old businessman with squeezing, band-like headaches that occur three or four times weekly. He rates the pain of these headaches as 7/10 and finds acetaminophen, aspirin, ibuprofen, naproxen, ketoprofen, and piroxicam only partly effective. He wants to take a prophylactic drug to prevent his headache disorder. Which medication would be best for prophylaxis of his headaches?
    A. Propranolol.
    B. Topiramate.
    C. Amitriptyline.
    D. Rizatriptan.

23. D.S. is a 49-year-old male computer programmer who describes piercing right-eye pain and lacrimation several times a day for 2–3 days in a row. He will have no episodes for 2–3 weeks but will then have recurrent episodes. In the office, he receives oxygen by nasal cannula during an episode, and his pain is relieved. Which medication would be best for prophylaxis of his headaches?
    A. Atenolol.
    B. Valproate.
    C. Nortriptyline.
    D. Lithium.

24. M.K. is a 44-year-old woman with right-sided headaches of moderate intensity that are accompanied by severe nausea and vomiting. Which medication would be best for M.K.'s migraine headaches?
    A. Almotriptan.
    B. Naratriptan.
    C. Promethazine.
    D. Sumatriptan.

25. T.C. is a 30-year-old woman with migraine headaches. Sumatriptan 100 mg provides immediate relief. However, about 2 hours later, her headache symptoms return. Which would be best for her?
    A. Rizatriptan 5 mg.
    B. Frovatriptan 2.5 mg.
    C. Naproxen 250 mg.
    D. Topiramate 25 mg.

V. MULTIPLE SCLEROSIS

A. Definitions
   1. Autoimmune disorder with areas of CNS demyelination and axonal transaction
   2. Clinical course
      a. Clinically isolated syndrome; first clinical presentation for which the 2017 diagnostic criteria for MS have not been met
      b. Classified as relapsing-remitting, secondary progressive, and primary progressive, with subclassification according to disease activity and progression: Relapsing-remitting: 85% of patients at diagnosis, develops into progressive disease in 50% of patients within 10 years

B. Epidemiology
   1. Diagnosis is usually at 20–50 years of age.
   2. Twice as many women as men develop MS.
   3. White people and people of northern European heritage are more likely to develop MS.
   4. Risk factors: Family history of MS, autoimmune disease, or migraine; personal history of autoimmune disease or migraine; cigarette smoke exposure, obesity (especially in childhood and adolescence), vitamin D deficiency, geography, genetic factors, Epstein-Barr virus

C. Treatment
   1. Acute relapses are treated with high-dose corticosteroids.
      a. Intravenous methylprednisolone: Usual dose is 500 mg to 1 g daily for 3–7 days (5 days typically), either alone or followed by an oral taper with prednisone.
      b. Oral prednisone: Usual dose is 1250 mg/day administered every other day for five doses.
      c. Intravenous adrenocorticotropic hormone
      d. Neurologic recovery is the same with or without an oral prednisone taper.
   2. Disease-modifying therapies (Table 9)
      a. Alemtuzumab (Lemtrada)
         i. Mechanism of action: Binds to CD52, a cell surface antigen on T cells, B cells, natural killer cells, monocytes, and macrophages; causes lysis of T and B cells
         ii. Adverse effects
            (a) Autoimmunity, including thyroid disorders (34%), immune thrombocytopenia, glomerular nephropathies
            (b) Infusion reactions (e.g., anaphylaxis, angioedema, bronchospasms, nausea, urticaria) occur in up to 92% of patients and necessitate corticosteroids during treatment.
            (c) Increased infections: Screen for herpes zoster and immunize, if needed; screen for tuberculosis before initiating therapy; prophylaxis for herpes infections is necessary during treatment.
            (d) May increase the risk of thyroid cancer, melanoma, and lymphoma
            (e) Administered only under a restricted distribution program
         iii. Avoid live virus vaccines during treatment; complete all vaccines 6 weeks before initiating therapy.
         iv. Avoid pregnancy during treatment and for 4 months after each treatment course.
      b. Beta-interferons (Avonex, Betaseron, Extavia, Plegridy, Rebif)
         i. Mechanism of action: Suppress T-cell activity, down-regulate antigen presentation by major histocompatibility complex class II molecules, decrease adhesion molecules and matrix metalloproteinase-9, increase anti-inflammatory cytokines, and decrease inflammatory cytokines
         ii. Adding polyethylene glycol to interferon beta-1a decreases the frequency of injections.

iii. Injection site reactions: More common in subcutaneously administered products. May help to bring a drug to room temperature before injection, ice the injection site, and rotate injection sites
iv. Flu-like symptoms: Usually dissipate in 2–3 months. May help to inject the dose in the evening. Begin at the 0.25- to 0.5-mg dose and slowly increase, and use ibuprofen or acetaminophen.
v. Neutralizing antibodies: Develop in some patients 6–18 months after treatment begins; frequency and administration route affect neutralizing antibody development; relapse rates are higher in patients with persistently high antibody titers; antibodies may disappear even during continued treatment; show cross-reactivity with other beta-interferons
vi. Avoid in severe, untreated depression.

c. Dimethyl fumarate (Tecfidera)
i. Mechanism of action: Antioxidant and cytoprotective; inhibits proinflammatory cytokines, increases anti-inflammatory cytokines
ii. Adverse effects
(a) Skin flushing: Occurs in up to 38% of patients, usually within 30–45 minutes of dosing; involves the face, chest, and neck; dissipates after 15–30 minutes; peaks within first month of therapy and decreases thereafter; aspirin may block flushing, taking with food helps prevent
(b) GI events: Occur in up to 41% of patients; peak within first month of therapy and decrease thereafter
(c) Lymphocytes decrease by 30% in the first year of therapy and then stabilize.
(d) Hepatotoxicity onset ranging from a few days to months after treatment initiation. Liver function test abnormalities resolve after therapy discontinuation.
iii. Indicated for use in pregnancy

d. Glatiramer acetate (Copaxone)
i. Mechanism of action: Decreases type 1 helper T cells; increases type 2 helper T cells; increases production of nerve growth factors
ii. Injection site reactions: Icing the site before and after injection and rotating the injection site may help.
iii. Systemic reactions: May involve flushing, chest tightness, palpitations, anxiety, and shortness of breath; this is noncardiac; recurrence is infrequent
iv. Avoid use in pregnancy unless clearly needed.

e. Fingolimod (Gilenya)
i. Mechanism of action: Binds to the sphingosine-1-phosphate receptor 1, 3, 4, 5 expressed on T cells, prevents activation of T cells
ii. Indicated for patients 10 years and older
iii. Contraindicated in patients with myocardial infarctions, unstable angina, stroke, TIAs, or decompensated heart failure necessitating hospitalization or class III/IV heart failure, history of Mobitz type II second- or third-degree atrioventricular block or sick sinus syndrome unless patient has a pacemaker, baseline QTc interval of 500 milliseconds or greater, or treatment with class Ia or class III antiarrhythmic drugs
iv. Patients must be monitored for bradycardia for 6 hours after the first dose; if therapy is discontinued for more than 2 weeks, patients must be re-monitored.
v. Adverse effects
(a) Bradycardia: ECG is recommended within 6 months for patients using antiarrhythmics (including β-blockers and calcium channel blockers), those with cardiac risk factors, and those with a slow or irregular heartbeat. Heart rate returns to baseline within 1 month of continued dosing.
(b) Atrioventricular conduction delays: First- and second-degree block

(c) Decrease in lymphocytes: A recent CBC should be available before therapy begins. Infections may be more common. Discontinue therapy for serious infections; test patients without varicella zoster vaccine or infection history for varicella zoster virus antibodies, and immunize antibody-negative patients (wait 1 month to initiate fingolimod).
(d) Macular edema: Ophthalmologic evaluation at baseline and 3–4 months after fingolimod initiation; a history of uveitis or diabetes increases risk
(e) Respiratory effects: Decreases in forced expiratory volume in 1 second and diffusion lung capacity for carbon monoxide can occur.
(f) Elevation of liver enzymes
(g) Hypertension: Monitor during treatment.
(h) Extended effects of drug for up to 2 months after discontinuation necessitate extended monitoring for many adverse effects.

vi. Drug interactions
(a) Ketoconazole: Increased fingolimod
(b) Vaccines: Less effective during and 2 months after fingolimod treatment; avoid live-attenuated vaccines

vii. Avoid pregnancy during treatment and for 2 months after treatment.
viii. Medication guide required

f. Mitoxantrone (Novantrone)
i. Mechanism of action: Decreases monocytes and macrophages, inhibits T and B cells
ii. Indicated for secondary progressive, primary progressive, and worsening relapsing-remitting MS; used infrequently because of toxicity
iii. Because of the potential for toxicity, mitoxantrone is reserved for patients with rapidly advancing disease whose other therapies have failed.
iv. Patients taking mitoxantrone should not receive live virus vaccines; other vaccines should be held for 4–6 weeks after dose.
v. Cardiotoxicity: Echocardiograms or multigated acquisition scans must be done at baseline and before each infusion. Systolic dysfunction occurs in about 12% of patients; congestive heart failure occurs in about 0.4%. Cardiotoxicity is not related to dose, sex, or age. Cyclooxygenase 2 inhibitors should be avoided; cumulative lifetime maximum dose of 140 mg/m^2
vi. Therapy-related acute leukemia occurs in about 0.8% of patients.
vii. Other laboratory tests (CBC, bilirubin, AST, ALT, ALP, and pregnancy test) must be done before each infusion.
viii. Avoid pregnancy during treatment.

g. Natalizumab (Tysabri)
i. Mechanism of action: Blocks T-cell entry into the CNS
ii. Indicated for relapsing forms of MS but distributed through restricted distribution program because of progressive multifocal leukoencephalopathy risk (0.24%)
iii. Adverse effects
(a) Hypersensitivity reactions: Itching, dizziness, fever, rash, hypotension, dyspnea, chest pain, anaphylaxis, usually within 2 hours of administration
(b) Progressive multifocal leukoencephalopathy: Rapidly progressive viral CNS infection; usually results in death or permanent disability. Patient selection guidelines are for patients with relapsing-remitting disease whose other treatment (efficacy or intolerability) has failed or who have an aggressive initial course; should not be used in combination with other disease-modifying therapies. On January 20, 2012, an FDA-issued drug safety communication stated that positive tests for John Cunningham virus (JCV) antibodies were a risk factor for progressive multifocal leukoencephalopathy. Thus, patients with all

three of the following risk factors – presence of anti-JCV antibodies, longer natalizumab treatment duration (especially beyond 2 years), and previous treatment with an immunosuppressive medication (mitoxantrone, azathioprine, methotrexate, cyclophosphamide, mycophenolate mofetil) – have a 1.1% chance of developing progressive multifocal leukoencephalopathy.
    (c) Antibodies to natalizumab, associated with increased relapses and hypersensitivity reactions, develop in 9%–12% of patients.
    (d) Severe liver toxicity, depression
    (e) Recent analysis found natalizumab may be used during pregnancy with patients at severe risk of disease reactivation during pregnancy.
    (f) REMS program required because of risk of progressive multifocal leukoencephalopathy associated with natalizumab

h. Ocrelizumab (Ocrevus)
    i. Mechanism of action: Thought to bind to CD20 on pre-B and mature B cells
    ii. Indicated for relapsing or primary progressive forms of MS
    iii. Pharmacokinetics: Two-compartment model with central compartment volume 2.78 L. Terminal half-life 26 days
    iv. Adverse effects
        (a) Infectious: Respiratory infections, herpes virus infections
        (b) Psychiatric: Depression
        (c) Infusion reactions
        (d) GI: Diarrhea
        (e) Malignancies
    v. Must test for hepatitis B before first dose, contraindicated if positive
    vi. Premedicate with methylprednisolone and an antihistamine before each infusion.
    vii. Administer necessary vaccines 4 weeks before dose (live, live-attenuated) or 2 weeks before dose (non-live).
    viii. Avoid pregnancy during treatment and for 6 months after treatment.
i. Ofatumumab (Kesimpta)
    i. Mechanism of action: Selectively targets and binds cell surface antigen CD20 on B cells, resulting in their depletion
    ii. Indication: Relapsing-remitting MS and secondary progressive disease
    iii. Contraindication: Active hepatitis B virus infection
    iv. Adverse effects:
        (a) Hepatitis B reactivation
        (b) Infection (upper respiratory tract infection)/reduction in immunoglobulins
        (c) Injection-related reactions – localized and systemic
        (d) Headache
    v. Avoid pregnancy during treatment and for 6 months after treatment.
j. Ozanimod (Zeposia)
    i. Mechanism of action: Sphingosine-1-phosphate receptor modulator
    ii. Indicated for relapsing forms of MS, including clinically isolated syndrome, relapsing-remitting, and active secondary progressive disease
    iii. Dose: Titrate dose to maintenance dose of 0.92 mg orally daily.
    iv. Contraindications: Within the past 6 months, patient has experienced a myocardial infarction, unstable angina, stroke, TIA, decompensated heart failure with hospitalization, class III or IV heart failure, Mobitz type II second-degree heart block, third-degree atrioventricular block, sick sinus syndrome, sinoatrial block, unless a functioning pacemaker

v. Adverse effects: Increased risk of infection, bradyarrhythmia and atrioventricular conduction delays, hepatotoxicity, teratogenicity, hypertension, decreased pulmonary function, macular edema, orthostatic hypotension
vi. Drug interactions: Avoid CYP2C8 inducers and inhibitors, BCRP inhibitors, and live-attenuated vaccinations.
vii. Avoid pregnancy during treatment and for 3 months after treatment.

k. Ponesimod (Ponvory)
i. Mechanism of action: Sphingosine-1-phosphate receptor modulator
ii. Indicated for treatment of relapsing forms of MS (including clinically isolated syndrome), relapsing-remitting disease, and active secondary progressive disease in adults
iii. Dose
(a) Initial: Administer once daily according to the 14-day dose titration shown in Table 8.

Table 8. Ponesimod Initial Dosage Titration

Day of Therapy	Dose (mg)
1 and 2	2
3 and 4	3
5 and 6	4
7	5
8	6
9	7
10	8
11	9
12, 13, and 14	10
15 and thereafter	20

(b) Maintenance: 20 mg once daily, beginning on day 15
iv. Contraindications
(a) In the past 6 months, patient has experienced myocardial infarction, unstable angina, stroke, TIA, decompensated heart failure requiring hospitalization, or class III or IV heart failure
(b) Presence of Mobitz type II second-degree, third-degree atrioventricular block, or sick sinus syndrome, unless patient has a functioning pacemaker
v. Drug interactions: Avoid immunosuppressive drugs and live vaccinations.
vi. Adverse reactions
(a) Transient, dose-dependent bradycardia; first-degree atrioventricular block; and hypertension have been observed primarily after the first dose of ponesimod and with dose titration.
(b) Cutaneous malignancies are rare.
(1) Basal cell carcinoma
(2) Malignant melanoma
(3) Squamous cell carcinoma
(c) Hepatotoxicity
(d) Increased risk of infection (e.g., upper respiratory tract, urinary tract, viral infections [herpes])
vii. Avoid pregnancy during treatment and for 1 week after treatment.

l. Teriflunomide (Aubagio)
   i. Mechanism of action: Prevents activation of lymphocytes
   ii. Indicated for relapsing forms of MS
   iii. Pharmacokinetics: Long half-life (18–19 days); takes about 3 months to reach steady-state concentrations; takes an average of 8 months to eliminate drug (serum concentrations less than 0.02 mcg/mL) and may take up to 2 years
   iv. Adverse effects
      (a) Hepatotoxicity may occur; teriflunomide should not be used in patients with preexisting liver disease or with ALT more than 2 times the upper limit of normal. Discontinue if severe liver damage occurs.
      (b) GI effects: Diarrhea, nausea
      (c) Dermatologic effects: Alopecia, rash (Stevens-Johnson syndrome)
      (d) Infection: Neutropenia and lymphopenia may occur; tuberculosis infections reported (negative tuberculosis skin test required at baseline); live virus vaccinations should not be administered
      (e) Teratogenic: Contraindicated in women of reproductive potential; negative pregnancy test at baseline; adequate contraception should be ensured; if pregnancy is desired for men or women, teriflunomide should be discontinued, accelerated elimination procedures should be undertaken, and two serum concentrations less than 0.02 mcg/mL taken 14 days apart should be confirmed
   v. Accelerated elimination procedures
      (a) Cholestyramine 8 g every 8 hours for 11 days (if not tolerated, may use 4 g)
      (b) Activated charcoal powder 50 g every 12 hours for 11 days

m. Siponimod (Mayzent)
   i. Mechanism of action: Sphingosine-1-phosphate receptor modulator, blocking the ability of lymphocytes to leave lymph nodes and enter systemic circulation
   ii. Indication: Clinically isolated syndrome; relapsing forms of MS, including relapsing-remitting; and active secondary progressive disease
   iii. Adverse effects
      (a) Common: Headache, hypertension, increased liver function tests
      (b) Serious: Infections, macular edema, bradyarrhythmia, atrioventricular conduction delays, decreased pulmonary function, hepatotoxicity
   iv. Contraindications:
      (a) *CYP2C9*3*3* genotype
         (1) Patients with this genotype possess decreased enzymatic activity, reducing the metabolism of siponimod, which can lead to substantially elevated siponimod plasma levels.
      (b) Myocardial infarction, unstable angina, stroke, TIA, decompensated heart failure, class III/IV heart failure in the past 6 months
      (c) Mobitz type II second-degree, third-degree atrioventricular block, sick sinus syndrome
   v. Drug interactions
      (a) Avoid live-attenuated vaccines during and up to 4 weeks after treatment.
      (b) CYP2C9 and CYP3A4 moderate or strong inhibitors and inducers should be avoided.
   vi. Avoid pregnancy during treatment and for 10 days after treatment.

n. Cladribine (Mavenclad)
   i. Mechanism of action: Not established for MS, but may be the result of cytotoxic effects on B and T lymphocytes
   ii. Indication: Relapsing forms of MS, including relapsing-remitting and active secondary progressive disease

iii. Adverse effects
(a) Common: Upper respiratory tract infection, headache, lymphopenia
(b) Serious: Hepatotoxicity, infection, graft-vs.-host disease after transfusion
iv. Contraindications: Current malignancy, women of reproductive potential, HIV infection, active chronic infections (e.g., hepatitis, tuberculosis), breastfeeding
v. FDA boxed warning: Contraindicated for use in women and men of reproductive potential who do not plan to use effective contraception because of the potential for fetal harm. Advise females and males of reproductive potential to use effective contraception during cladribine treatment and for 6 months after treatment.
vi. Drug interactions: Avoid immunosuppressive and antiviral/antiretroviral drugs, avoid live-attenuated vaccinations, hematotoxic drugs

o. Ublituximab-xiiy (Briumvi)
i. Mechanism of action: Precise mechanism unknown; likely involves binding to CD20, a cell surface antigen presented on pre-B and mature B lymphocytes, and causing cell lysis
ii. Indication: Treatment of relapsing forms of multiple sclerosis
iii. Adverse effects: Infusion reactions, upper respiratory tract infections, lower respiratory tract infections, herpes virus-associated infections
iv. Contraindications: Active hepatitis B virus infection
v. Precautions: Vaccination with live-attenuated or live vaccines is not recommended during treatment
vi. Special considerations:
(a) Closely monitor during and for at least 1 hour after completing first 2 infusions.
(b) Premedicate before every infusion to reduce frequency and severity of infusion reactions with methylprednisolone and diphenhydramine (orally/intravenously).
(c) Females of reproductive potential should use effective contraception during treatment and for 6 months after final dose.

3. Symptomatic therapies
a. Patients may have fatigue, spasticity, urinary incontinence, pain, depression, cognitive impairment, fecal incontinence, constipation, pseudobulbar affect, and sexual dysfunction; standard therapies should be used for these symptoms.
b. Fatigue: Treatment may be nonpharmacologic (rest, assistive devices, cooling strategies, exercise, stress management) or pharmacologic (amantadine, methylphenidate, modafinil, fluoxetine).
c. Spasticity: Therapies must be centrally acting.
i. First line: Baclofen, tizanidine
ii. Second line: Dantrolene, diazepam
iii. Third line: Intrathecal baclofen, gabapentin
iv. Focal spasticity: Botulinum toxin
d. Walking impairment: Dalfampridine (Ampyra)
i. Indicated to improve walking in patients with MS by improving walking speed
ii. Potassium channel blocker, prolongs action potentials in demyelinated neurons
iii. Dose: 10 mg orally twice daily; extended-release tablets
iv. Contraindicated in patients with a history of seizures or moderate or severe renal impairment
v. Adverse effects: Seizures, UTIs, insomnia
e. Pseudobulbar affect: Dextromethorphan/quinidine
i. Affects 10% of patients
ii. Episodes of inappropriate laughing or crying
iii. Dextromethorphan prevents excitatory neurotransmitter release.
iv. Low-dose quinidine blocks first-pass metabolism of dextromethorphan, thus increasing dextromethorphan serum concentrations.

Table 9. Comparison of Disease-Modifying Therapies

Generic (Brand)	Dose	Route	Frequency	Adverse Effects
Alemtuzumab (Lemtrada)	First course: 12 mg/day over 4 hr × 5 days Second course: 12 mg/day over 4 hr × 3 days 12 mo after first course	IV	Daily for 5 days; then daily for 3 days 12 mo later	Infusion reaction 92% Rash 53% Thyroid disorders 34% Headache 52% Infections 13%–19%
Cladribine (Mavenclad)	Recommended cumulative dose 3.5 mg/kg orally divided into 2 yearly courses. See labeling for detailed administration schedule	PO	Two cycles annually	Upper respiratory tract infection 38% Headache 25% Lymphopenia 24%
Dimethyl fumarate (Tecfidera)	120 mg twice daily × 7 days; then 240 mg twice daily	PO	Twice daily	Skin flushing 38% GI events 41%
Fingolimod (Gilenya)	0.5 mg	PO	Daily	Increased AST/ALT 14% Infections 13% Diarrhea 12% Hypertension 6% Bradycardia 4% Blurred vision 4% Lymphopenia 4% Leukopenia 3%
Glatiramer acetate (Copaxone)	20 mg 40 mg	SC	Daily Three times/wk	Injection site reaction 90% Systemic reaction 15%
Interferon beta-1a (Avonex)	30 mcg	IM	Weekly	Flu-like symptoms 61% Anemia 8% Depression
Interferon beta-1a (Rebif)	22 mcg or 44 mcg	SC	Three times/wk	Flu-like symptoms 28% Injection site reactions 66% Leukopenia 22% Increased AST/ALT 17%–27% Depression
Interferon beta-1b (Betaseron)	0.25 mg	SC	Every other day	Flu-like symptoms 60%–76% Injection site reactions 50%–85% Asthenia 49% Menstrual disorder 17% Leukopenia 10%–16% Increased AST/ALT 4%–19%
Mitoxantrone (Novantrone)	12 mg/m2 Up to 140 mg/m^2 (lifetime dose)	IV	Every 3 mo	Nausea 76% Alopecia 61% Menstrual disorders 61% UTI 32% Amenorrhea 25% Leukopenia 19% Increased γ-Glutamyl transpeptidase 15%

Table 9. Comparison of Disease-Modifying Therapies (*Cont'd*)

Generic (Brand)	Dose	Route	Frequency	Adverse Effects
Natalizumab (Tysabri)	300 mg	IV	Every 4 wk	Headache 38% Fatigue 27% Arthralgia 19% UTI 20% Hypersensitivity reaction < 1% Progressive multifocal leukoencephalopathy
Ocrelizumab (Ocrevus)	300 mg, followed by 300 mg 2 wk later; then 600 mg	IV	Every 6 mo after initial doses	Injection site reactions 34% Risk of infection
Ofatumumab (Kesimpta)	Initial: 20 mg at week 0, 1, 2 Maintenance: 20 mg at week 4 and then monthly	SC	Weekly × 3 doses; then on week 4; then monthly	Infection 52% Injection site reactions 21% Headache 13%
Pegylated interferon beta-1a (Plegridy)	125 mcg	SC	Every 2 wk	Injection site reactions 62% Flu-like symptoms 47% Headache 44% Myalgia 19%
Ponesimod (Ponvory)	Initial: Administer once daily according to a 14-day dose titration (in Table 8) Maintenance: 20 mg once daily, beginning on day 15	PO	Once daily	Hepatic: Increased serum transaminases 23%; increased serum alanine aminotransferase (≥ 5 × upper limit of normal) 5%; ≥ 3 × upper limit of normal: 17%) Infection: 54%; serious or severe infection: ≤ 2% Respiratory: Upper respiratory tract infection 37%
Siponimod (Mayzent)	Depending on *CYP2C9* genotype, usual dose titrate over 5 days to 1 mg	PO	Daily	Headache 15% Hypertension 13% Increased liver function tests 11% Falls 11% Peripheral edema 8% Nausea 7% Dizziness 7% Diarrhea 7% Bradycardia 6% Pain 6%
Teriflunomide (Aubagio)	7 mg or 14 mg	PO	Daily	Diarrhea 15%–18% Nausea 9%–14% Alopecia 10%–13% Neutropenia 10%–15% Lymphopenia 7%–10% Elevated ALT 3%–5% Hypertension 4% Peripheral neuropathy 1%–2% Reactivation of tuberculosis
Ublituximab-xiiy (Briumvi)	150 mg on day 1, followed by 450 mg once 2 weeks later; then 450 mg every 24 weeks after the first 150 mg dose	IV	Every 24 weeks after initial doses	Infusion reactions 48% Upper respiratory tract infections 45% Lower respiratory tract infections 9% Herpes virus-associated infections 6%

IM = intramuscular(ly); IV = intravenous(ly); PO = oral(ly); SC = subcutaneous(ly).

Patient Cases

Questions 26–28 pertain to the following case:

S.F. is a 36-year-old woman with a history of MS. This morning, her left arm became progressively weaker over about 3 hours. She was previously healthy except for a broken radius when she was 13 years old and a case of optic neuritis when she was 25. Her current medications include metoprolol 100 mg orally twice daily and fluoxetine 10 mg orally daily.

26. Which would be best for treating S.F.'s exacerbation?
    A. Interferon beta-1a.
    B. Glatiramer acetate.
    C. Methylprednisolone.
    D. Fingolimod.

27. Which would be best for S.F. to prevent further exacerbations?
    A. Methylprednisolone.
    B. Baclofen.
    C. Glatiramer acetate.
    D. No treatment.

28. S.F. elects to start fingolimod. Which would be best to monitor every 6 months while she is taking fingolimod?
    A. ECG.
    B. Sodium.
    C. Pulmonary function tests.
    D. Renal function tests.

29. B.B. is a 33-year-old woman with recently diagnosed MS. Her neurologist wants you to discuss with her the potential medications to prevent exacerbations. During the discussion, you find that she and her husband are planning to have a child in the next few years and that she is frightened of needles. Which would be best for B.B.?
    A. Glatiramer acetate.
    B. Mitoxantrone.
    C. Teriflunomide.
    D. Dimethyl fumarate.

VI. PERIPHERAL NEUROPATHY

A. Broad range of diseases that damage nerves outside the brain and spinal cord. Other terms for peripheral neuropathy include *peripheral neuritis*, *polyneuropathy*, and *polyneuritis*.
    1. More than 100 types; each is unique
    2. Can be classified as acute or chronic; also, can be predominantly motor, mixed motor and sensory, or predominantly sensory

B. Epidemiology
   1. 30 million people in the United States have some form of peripheral neuropathy.
   2. The most common form is diabetic neuropathy. Diabetic peripheral neuropathy can occur before an official diagnosis of diabetes and may be the presenting symptom of diabetes.

C. Clinical Course
   1. Patients may initially present with altered sensation, pain, weakness, or autonomic symptoms. Symptoms typically are present distally in the initial stages.
   2. Symptoms may be bilateral or unilateral, symmetrical, or asymmetrical.
   3. Symptoms progress proximally. In advanced stages, distal wasting, weakness, absent deep tendon reflexes, and glove and stocking sensory loss can occur.

D. Diagnosis
   1. Complete medical history, medication history, and neurologic examination
   2. Electromyelogram and nerve conduction studies
   3. Laboratory tests to include serum chemistry, CBC, toxicology screen, vitamin B_{12} concentration, immune panel

E. Causes

Table 10. Common Causes of Acute Severe Peripheral Neuropathy

Cause	Predominantly Motor	Mixed	Predominantly Sensory
Guillain-Barré syndrome	+	+	—
Vasculitis	—	+	—
Diabetes	—	+	+
Drugs[a]	—	+	+
Porphyria	+	—	—
Diphtheria	—	+	—
Paraneoplastic neuropathy	—	+	+
Acute idiopathic sensory neuropathy	—	—	+
Critical illness	+	+	—
Chronic inflammatory demyelinating polyneuropathy	—	+	—

[a]Examples include nitrofurantoin, vincristine, cisplatin, and reverse transcriptase inhibitors.

F. Treatments
   1. Most treatments are directed toward symptomatic relief of the sensory component of neuropathies.
   2. Systemic and topical treatments may be combined.
   3. If an immune component is involved, treatments include immune modulation. Recommendations for specific regimens vary with the disease diagnosis.
      a. Prednisone
      b. Immunoglobulin
      c. Plasmapheresis
      d. Immunosuppressants (e.g., cyclosporine, azathioprine, tacrolimus, sirolimus)

Table 11. Pharmacotherapy for Neuropathic Pain

Therapy	Route	Starting Dose	Maintenance Dose
ORAL AGENTS			
First Line			
Tricyclic antidepressants (TCAs) • Nortriptyline • Amitriptyline	PO	10–25 mg at bedtime	Increase by 10- to 25-mg increments to 150 mg at bedtime
Gabapentinoids • Gabapentin	PO	600 mg three times daily	Increase by 300- to 400-mg increments to 3600 mg/day in three or four doses
• Pregabalin	PO	25 mg daily or 50–150 mg/day in two or three divided doses	Increase by 25–150 mg/day at weekly intervals depending on response. Usual dose: 300–600 mg/day in two or three divided doses
Serotonin-norepinephrine reuptake inhibitors (SNRIs) • Duloxetine	PO	30 mg daily	Increase by 30- to 60-mg increments up to 60 mg daily
• Venlafaxine	PO	37.5 mg daily	Increase by 75-mg increments to 225 mg/day
Lidocaine 5%	Topical	Apply patch or cream over the site of pain 12 hr on, 12 hr off	Increase up to 3 patches worn for up to 12 hr daily
Capsaicin 8%	Topical	Apply to affected region for 60 min	Continue starting dose
Second Line			
Tramadol	PO	50 mg two or four times daily	Increase by 50-mg increments to a maximum of 100 mg four times daily
Combination therapy • Gabapentinoid + TCA	PO	Only use if single agents provided inadequate relief and no adverse effects	
• Gabapentinoid + SNRI	PO	Titrate as indicated for single agent. Aim for lower doses of both agents	
Third Line			
Carbamazepine	PO	200 mg twice daily	Increase by 200-mg increments to 200–400 mg three or four times daily; follow serum concentrations on doses greater than 600 mg/day
Lamotrigine	PO	25 mg once daily	Increase by 25-mg increments weekly to 100–200 mg twice daily
Topiramate	PO	25–50 mg at bedtime	Increase by 50-mg increments weekly to 200 mg twice daily
Valproate	PO	250 mg two or three times daily	Increase by 250-mg increments up to 1500 mg/day
Fourth Line			
Low-dose opioids • Oxycodone • Morphine • Methadone • Levorphanol	PO	• Should not be considered until exhausting all pharmacotherapy options above and neurostimulation therapy • Lack of long-term efficacy data and significant adverse effects limit their usefulness • 10–15 mg of morphine every 4 hr or PRN (equianalgesic dosages should be used for other opioid dosing)	
Newer Drugs			
Milnacipran	PO	12.5 mg at bedtime for 1 day	12.5 mg twice daily for 2 days; then 25 mg twice daily for 4 days; then 50 mg twice daily. May increase up to 100 mg twice daily
Lacosamide	PO	50 mg twice daily	Increase to 100 mg twice daily after 1 wk. May increase up to 200 mg twice daily

Table 11. Pharmacotherapy for Neuropathic Pain (*Cont'd*)

Therapy	Route	Starting Dose	Maintenance Dose
TOPICAL AGENTS			
OTC			
Capsaicin 0.075%	Topical	Apply to affected region three or four times daily	Continue starting dose
Diclofenac sodium gel 1%	Topical	Apply to affected region three or four times daily	Continue with starting dose
Salicylate 10%–25%	Topical	Apply to affected region three or four times daily	Continue starting dose
Menthol 16%/ camphor 3%	Topical	Apply to affected region three or four times daily	Continue with starting dose
Prescription			
Lidocaine 2.5%/ prilocaine 2.5%	Topical	Apply to affected region three or four times daily	Continue with starting dose
Doxepin 5%	Topical	Apply to affected region twice daily	Continue with starting dose
Diclofenac sodium gel 1%	Topical	Apply to affected region three or four times daily	Continue with starting dose
Compounded Prescription Products			
Ketoprofen 5%/ amitriptyline 2%/ tetracaine 1%	Topical	Apply to affected area twice daily	Increase up to four times daily
Ketoprofen 10%/ cyclobenzaprine 1%/ lidocaine 5%	Topical	Apply to affected region twice daily	Increase up to four times daily
Ketamine 5%/ amitriptyline 4%/ gabapentin 4%	Topical	Apply to affected region twice daily	Increase up to thrice daily
Carbamazepine 5%/ lidocaine 5%	Topical	Apply to affected region twice daily	Increase up to four times daily
Amitriptyline 2%/ baclofen 2%	Topical	Apply to affected region three or four times daily	Continue with starting dose

PO = oral(ly); PRN = as needed.

Patient Cases

Questions 30 and 31 pertain to the following case.

S.B. is a 55-year-old man referred to a neurologist for numbness, burning, and tingling in his feet that have progressively worsened over the past year. On neurologic examination, he has decreased sensations bilaterally to the mid-calf. He takes no medications except for nonprescription analgesics as needed for pain. His BMI is 32 kg/m^2.

30. Which laboratory test would best determine the cause of S.B.'s neuropathy?
    A. Potassium.
    B. A1C.
    C. Serum creatinine.
    D. WBC.

31. Which therapy would be best for S.B.?
    A. Naproxen.
    B. Tramadol.
    C. Nortriptyline.
    D. Prednisone.

32. A meta-analysis of treatments for neuropathic pain included data from 26 clinical trials (MedGenMed 2007;9:36). The results of the review included the following data.

Treatment	No. Needed to Treat
Tricyclic antidepressants	2.1
SNRIs	5.1
SSRIs	7

    Given these data, which would be most effective for neuropathic pain?
    A. Duloxetine.
    B. Sertraline.
    C. Amitriptyline.
    D. Venlafaxine.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: D
Generalized motor myoclonic-type seizures can be treated in several ways; the best option in this case is levetiracetam (Answer D), which is effective for generalized motor myoclonic-type epilepsy and has much less risk of teratogenic effects. Phenytoin (Answer B) and phenobarbital (Answer C) are considered second-line treatments for generalized motor myoclonic-type seizures and can reduce the effectiveness of oral contraceptives. Although valproate (Answer A) is effective for generalized motor myoclonic-type seizures, it is associated with several teratogenic effects. Because this patient is a woman of childbearing potential, it is advisable to avoid valproate even though she takes oral contraceptives.

2. Answer: A
Interactions with oral contraceptives are a concern with several ASMs. In these cases, alternative forms of birth control (Answer B) may be necessary. Decreased effectiveness of oral contraceptives may be associated with breakthrough bleeding (Answer C). In addition, oral contraceptives can alter the effectiveness of ASMs (Answer D). However, no evidence supports that levetiracetam alters oral contraceptive effectiveness or that oral contraceptives change the effectiveness of levetiracetam, making Answer A correct.

3. Answer: A
Rufinamide (Answer B) is not first line for treating generalized motor myoclonic-type seizures; instead, it is indicated for first-line treatment of Lennox-Gastaut syndrome. Cannabidiol (Answer C) has only been shown effective in Dravet syndrome and Lennox-Gastaut syndrome. Valproate (Answer D) should be avoided in this patient because of its teratogenic adverse effects. Lamotrigine (Answer A) is a reasonable alternative that is first line for treating generalized motor myoclonic-type seizures and is not associated with an increased risk of teratogenic adverse effects; however, the potential for reduced oral contraceptive effectiveness should be discussed.

4. Answer: B
Lorazepam (Answer B) is the drug of choice for status epilepticus. Lorazepam is less lipophilic than diazepam (Answer A); therefore, lorazepam does not redistribute from the CNS as quickly. Phenytoin (Answer C) and phenobarbital (Answer D) should be held in reserve for maintenance therapy or refractory status epilepticus.

5. Answer: D
Phenytoin has nonlinear pharmacokinetics. A small increase in dose may result in a large increase in serum concentration. Therefore, without doing any calculations, we can surmise that an increase from 300 mg/day to 600 mg/day would more than double the serum concentration (Answer D). Lower increases (Answers A–C) would be unlikely with an increase in dose this large.

6. Answer: D
Phenytoin (Answer A) and carbamazepine (Answer C) can increase absence seizure frequency. Valproate (Answer B), though an alternative, is less desirable because of its adverse effect profile. Ethosuximide (Answer D) is useful for absence seizures and had fewer adverse effects than valproate in a randomized study.

7. Answer: D
Although hepatotoxicity (Answer A) is a possible adverse effect of carbamazepine, it is most likely to occur within the first few months of starting carbamazepine. Acne (Answer B) and gingival hyperplasia (Answer C) are adverse effects associated with phenytoin. Diplopia (Answer D) is a common adverse effect associated with higher concentrations of carbamazepine.

8. Answer: C
Hepatoxicity (Answer A) is associated with several ASMs but not with levetiracetam. Alopecia (Answer D) is a common adverse effect of valproate. Depression (Answer C) and agitation are common adverse effects of levetiracetam. Zonisamide is associated with a 1% increase in the risk of renal stones (Answer B).

9. Answer: D
Carbamazepine forms an active epoxide intermediate (carbamazepine-10,11-epoxide), whereas oxcarbazepine does not (Answer D). Carbamazepine induces more liver enzymes than oxcarbazepine (Answer A). However, hyponatremia is more closely associated with oxcarbazepine than with carbamazepine (Answer C). Both carbamazepine and oxcarbazepine can cause allergic rashes (Answer B).

10. Answer: C
Immediate discontinuation of oxcarbazepine (Answer A) would likely increase seizures. Topiramate (Answer B) is associated with an increased risk of teratogenic adverse effects. Lamotrigine (Answer D) is considered safe during pregnancy, but changing medications increases the risk of seizures. In addition, lamotrigine pharmacokinetics change during pregnancy, complicating its management. Continuing the patient's current medication (Answer C) is the best approach during pregnancy.

11. Answer: D
Nonmodifiable risk factors for stroke include age, race, and male sex. Somewhat modifiable risk factors include hypercholesterolemia and diabetes. Modifiable stroke risk factors include hypertension, smoking, and atrial fibrillation. Less well-documented risk factors include obesity, physical inactivity, alcohol abuse, hyperhomocystinemia, hypercoagulability, hormone replacement therapy, and oral contraceptives. Minimal cognitive impairment (Answer C) and osteoarthritis (Answers A and B) are not risk factors for stroke. Answer D is the only option that includes only risk factors for stroke.

12. Answer: C
There are many contraindications to administering tissue plasminogen activator for stroke, mainly focused on bleeding risk. There is no upper limit on age (Answer B). Breast cancer (Answer D) is not a contraindication for tissue plasminogen activator. The patient's symptoms began 6 hours ago, placing her outside the window for alteplase use (Answer C is correct; Answer A is incorrect).

13. Answer: C
Warfarin (Answer D) is only indicated for stroke prevention with atrial fibrillation. Other than modifying a partly modifiable risk factor for stroke, metformin (Answer A) has no benefit in preventing stroke. Celecoxib (Answer B) also has no benefit in preventing stroke and, according to some studies, may increase the risk of stroke. Aspirin and clopidogrel (Answer C) should be used together for 21 days after a minor acute stroke to reduce the risk of another stroke.

14. Answer: D
This patient was diagnosed with a minor stroke, according to the neurology team. Dual antiplatelet therapy should be initiated within 24 hours of a minor stroke and continued for 21 days. After the 21 days of DAPT, the patient should be transitioned to single antiplatelet therapy, which should be continued indefinitely. Answer A is incorrect; DAPT should be continued for 21 days, not 90 days, after a (minor) stroke. Answer B is incorrect; DAPT should not be continued as chronic therapy because the patient has been receiving it for 60 days, which exceeds the 21-day recommendation. Single antiplatelet therapy should be continued indefinitely, not just for 90 days, making Answer C incorrect and Answer D correct.

15. Answer: D
With a mitral valve replacement, the target INR is 2.5–3.5, making 3 (Answer D) an optimal target. An INR of 1.5 (Answer A) or 2 (Answer B) is too low for a valve replacement. An INR of 2.5 (Answer C) is at the bottom of the acceptable target range, making it difficult to consistently keep her INR in the range.

16. Answer: A
Anticholinergic drugs like trihexyphenidyl only control tremor – not other symptoms of Parkinson disease. Increasing the trihexyphenidyl dose (Answers B and D) would not improve control of his symptoms and would increase anticholinergic adverse effects. Decreasing the carbidopa/levodopa dose (Answer C) would worsen his Parkinson disease symptoms. Increasing the carbidopa/levodopa dose and discontinuing trihexyphenidyl (Answer A) should improve all of his symptoms and reduce any anticholinergic adverse effects.

17. Answer: D
Wearing-off phenomenon is the return of Parkinson disease symptoms before the next dose. This problem can be resolved by administering doses more often (Answer D), administering the controlled-release formulation of carbidopa/levodopa, or adding a COMT inhibitor. Increasing the dosing interval (Answer C) means that doses are administered further apart. Increasing the dose (Answer A) would not address wearing-off at the end of a dosing interval and would place the patient at risk of developing dyskinesia. Decreasing the dose (Answer B) would cause the patient's Parkinson symptoms to worsen.

18. Answer: B
Entacapone (Answer B) can cause a reddish orange discoloration of the urine. Amantadine (Answer C)

can cause a reddish brown skin discoloration, but not changes in the urine. Carbidopa/levodopa (Answer A) does not cause changes in the urine. Cystitis (Answer D) is a possibility, but entacapone more likely caused the change in urine color.

19. Answer: D
Ropinirole (Answer A) helps with the initial treatment of Parkinson disease, but adding it to the patient's current regimen without adjusting the carbidopa/levodopa dose would worsen his dyskinesia. Selegiline (Answer B) would not address his dyskinesia and could make it worse by decreasing the breakdown of levodopa. Increasing the carbidopa/levodopa dose (Answer C) would make his dyskinesia worse. Decreasing the carbidopa/levodopa dose (Answer D) will improve the dyskinesia.

20. Answer: C
Trihexyphenidyl (Answer A) is only effective for tremors in Parkinson disease and has anticholinergic adverse effects. In this patient, it would not treat the other symptoms of the disease, and anticholinergic adverse effects are not advisable in an older individual. Carbidopa/levodopa (Answer C) is efficacious as monotherapy for symptomatic Parkinson disease. Istradefylline (Answer D) is an adjunct to carbidopa/levodopa. Apomorphine (Answer B) is for the acute treatment of off-episodes and not clinically useful for symptomatic Parkinson disease as monotherapy.

21. Answer: A
A β-blocker (Answer A) is a good choice for a patient with coexisting hypertension. Indomethacin (Answer B) can be used for migraine, but it is held in reserve because of serious adverse effects. Although topiramate (Answer C) might decrease the patient's weight, it has an increased risk of teratogenic adverse effects. Sumatriptan (Answer D) is for the acute treatment of migraine headaches, not for prophylaxis.

22. Answer: C
Amitriptyline (Answer C) is effective as prophylaxis for tension headaches. Propranolol (Answer A) and topiramate (Answer B) are usually used for migraine headache prophylaxis. Rizatriptan (Answer D) is an acute treatment for migraine headaches.

23. Answer: D
Lithium (Answer D) is a prophylactic agent for cluster headaches. Atenolol (Answer A) and valproate (Answer B) are usually used for migraine headache prophylaxis. Nortriptyline (Answer C) is useful for migraine and tension headaches.

24. Answer: D
Sumatriptan (Answer D) is available as both an injectable and a nasal spray and would be appropriate to use in a patient with severe nausea and vomiting. Almotriptan (Answer A) and naratriptan (Answer B) only come in oral dosage forms and would not be optimal in the face of nausea and vomiting. Promethazine (Answer C) might reduce nausea and vomiting but would not treat the patient's migraine headache.

25. Answer: B
Topiramate (Answer D) is used as a prophylactic drug and not in the acute treatment of a migraine. Naproxen (Answer C) would be less likely to relieve her headache without being combined with a triptan. Rizatriptan (Answer A) has a short half-life, making it less effective 2 hours later. Frovatriptan (Answer B) has a longer half-life, making it more likely to prevent the headache from returning 2 hours later.

26. Answer: C
Methylprednisolone (Answer C) is the only option used for acute exacerbations. Interferon beta-1a (Answer A), glatiramer acetate (Answer B), and fingolimod (Answer D) are all used as disease-modifying therapies.

27. Answer: C
Glatiramer acetate (Answer C) is an appropriate initial choice for disease-modifying therapy. Methylprednisolone (Answer A) is only for exacerbations. Baclofen (Answer B) is only for spasticity and does not have disease-modifying properties. Providing no treatment (Answer D) would be unacceptable because of the patient's many episodes of exacerbations.

28. Answer: A
Fingolimod (Answer A) is associated with cardiac arrhythmias, and the ECG should be monitored at least every 6 months. Sodium (Answer B), pulmonary function tests (Answer C), and renal function tests (Answer D) do not need to be routinely monitored with fingolimod.

29. Answer: D

Glatiramer (Answer A) is not the best option because the patient is frightened of needles and glatiramer is an injectable; also, glatiramer should be avoided in pregnancy, if possible. Mitoxantrone (Answer B) has significant toxicities and is contraindicated in pregnancy. Teriflunomide (Answer C) is also contraindicated in pregnancy. Dimethyl fumarate (Answer D) is a pregnancy category C drug. However, this patient should carefully plan her conception and can discontinue the medication before pregnancy.

30. Answer: B

The most likely cause of peripheral neuropathy in this patient is diabetes, even if this was not previously diagnosed. Therefore, A1C (Answer B) is the most useful laboratory value for determining the potential cause. Potassium (Answer A), serum creatinine (Answer C), and WBC (Answer D) do not help determine the cause of neuropathy.

31. Answer: C

Naproxen (Answer A) would unlikely be beneficial because the patient has been taking nonprescription analgesics without symptom relief. Although tramadol (Answer B) is a possibility, it is usually considered second line for peripheral neuropathy. Prednisone (Answer D) is not typically used for the initial treatment of neuropathy. Prednisone can be used in very specific immunologic neuropathies, but these are unlikely in this scenario. Nortriptyline (Answer C) is considered a first-line treatment for peripheral neuropathy. Given that the patient has not previously been treated, it is the best initial treatment.

32. Answer: C

Number needed to treat (NNT) is an estimate of the number of patients who would need to receive treatment for one patient to benefit. Therefore, the lower the NNT, the more likely a treatment is to be effective. Tricyclic antidepressants, including amitriptyline (Answer C), have the lowest NNT value in this comparison, so they are most likely to be effective. Duloxetine (Answer A) and venlafaxine (Answer D) are less likely to effective. Sertraline (Answer B) is the least likely to be effective.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: B
This patient most likely has focal epilepsy, given the description of his spells and the EEG. Ethosuximide (Answer A) has a very narrow spectrum of generalized nonmotor seizures, making it incorrect. Phenobarbital (Answer C) has common or severe adverse effects, making it less than optimal as initial pharmacotherapy. Clobazam (Answer D) is indicated only for Lennox-Gastaut syndrome. Levetiracetam (Answer B) is indicated for monotherapy for focal seizures and has fewer adverse effects than phenobarbital and clobazam.

2. Answer: C
With a blood glucose of less than 60 mg/dL, hypoglycemia could be a cause of this patient's status epilepticus. Although lorazepam (Answer A) and diazepam (Answer D) are appropriate for treating seizures not caused by hypoglycemia, a possible hypoglycemic episode must be treated first. Because the patient's nutritional status is unknown, she could be thiamine deficient. Administering dextrose (Answer B) in the face of thiamine deficiency could precipitate an encephalopathy. Thiamine (Answer C) should be administered before dextrose.

3. Answer: A
Agitation and depression are common adverse effects of levetiracetam. Because of the patient's wife's concerns for his irritability and depression, it is probably advisable to discontinue levetiracetam (Answer A) and change to a different ASM. Increasing the dose (Answer B) could worsen his symptoms, and his symptoms are probably not the result of ongoing seizures. Continuing levetiracetam (Answer C) might be an alternative, but given that he and his spouse have concerns for adverse effects, it is a less-than-optimal approach. No clear correlation has been established between efficacy or toxicity and levetiracetam concentrations (Answer D). Therefore, a concentration would not help guide therapeutic decisions.

4. Answer: B
The most critical test before initiating treatment for stroke is head imaging. A CT scan of the head (Answer B) allows the clinician to distinguish between an ischemic stroke and a hemorrhagic stroke. A cerebral angiogram (Answer A) may be helpful later to determine whether there is a lesion in the cerebral vasculature, but it is not essential in the acute setting. A coagulation panel (Answer C) is not necessary to determine whether to initiate alteplase in the acute setting. Similarly, an echocardiogram (Answer D) may be useful in a patient's diagnostic workup after a stroke, but it is not necessary in the acute care setting.

5. Answer: A
A combination of aspirin and clopidogrel is indicated for 90 days after a major ischemic stroke (Answer A). A combination of aspirin and dipyridamole (Answer B) is a possible treatment for long-term stroke prophylaxis (after the 90-day DAPT with aspirin and clopidogrel). Apixaban (Answer C) is only indicated for prophylaxis in the setting of atrial fibrillation, which this patient does not have. Warfarin (Answer D) is only indicated for prophylaxis of stroke in atrial fibrillation or mechanical mitral valve replacement.

6. Answer: D
Gait disturbances (Answer A), falls (Answer B), and handwriting (Answer C) are not improved by use of levodopa or a dopamine agonist. Rigidity (Answer D) is improved with levodopa or a dopamine agonist.

7. Answer: B
This patient is experiencing wearing-off before the next dose. A COMT inhibitor, entacapone (Answer B), slows the degradation of dopamine in the synaptic cleft and extends the effectiveness of levodopa. Istradefylline (Answer A) is adenosine receptor antagonist that may be used as an adjunct to carbidopa/levodopa and treats off-episodes. Apomorphine (Answer C) is indicated for on-off phenomenon but is not indicated for wearing-off before the next dose. Quetiapine (Answer D) is a preferred antipsychotic to manage hallucinations secondary to Parkinson disease itself or adverse effects of dopamine agonists.

8. Answer: D
Many medications used for nausea, including metoclopramide (Answer B) and promethazine (Answer A), are dopamine antagonists and potentially worsen nausea and vomiting. Reducing carbidopa/levodopa (Answer C) would likely worsen Parkinson symptoms. Trimethobenzamide (Answer D) is a selective

antagonist for the D_2 receptor, making it less likely to worsen Parkinson symptoms.

9. Answer: A
This patient most likely has tension headaches, given his description of the headaches. The most effective medication for acute treatment of tension headaches is naproxen (Answer A). Sumatriptan (Answer B) and dihydroergotamine (Answer C) are indicated for acute treatment of migraine-type headaches. Lithium (Answer D) is only used to prevent cluster headaches.

10. Answer: A
This patient most likely has a tension-type headache. Amitriptyline (Answer A) is effective for preventing tension-type headaches. Valproate (Answer B) and topiramate (Answer C) are not used to prevent tension-type headaches. Frovatriptan (Answer D) is only indicated for the acute treatment of migraine.

11. Answer: D
Fingolimod (Answer D) is the only choice with an FDA indication for the treatment of MS. In addition, fingolimod has the best clinical trial evidence of efficacy. Methylprednisolone (Answer B) is used for acute MS exacerbations. Cyclophosphamide (Answer A) and azathioprine (Answer C) have been studied in progressive forms of MS, but their data are not as robust as those for fingolimod.

12. Answer: B
Treatment of spasticity in MS requires a centrally acting agent. Of the choices, only diazepam (Answer A) and baclofen (Answer B) are centrally acting. Because of the significant fatigue and drowsiness that occur with diazepam, baclofen is usually a first-line therapy. Carisoprodol (Answer C) and metaxalone (Answer D) are indicated for muscle spasms, but not spasticity.

13. Answer: C
Amantadine (Answer C) is used in MS for fatigue. Propranolol (Answer A), lamotrigine (Answer B), and ropinirole (Answer D) are not used in MS.

14. Answer: A
Diabetic neuropathy (Answer A) is the most common cause of peripheral neuropathy and may occur even before a patient is diagnosed with diabetes. Chronic inflammatory demyelinating polyneuropathy (Answer B) and genetic neuropathy (Answer D) are much less common, and symptoms are not consistent with this presentation. An entrapped nerve (Answer C) would typically be unilateral.

15. Answer: B
Carbamazepine (Answer A) and valproate (Answer D) are considered third-line medications for diabetic neuropathy pain. Acetaminophen (Answer C) would unlikely relieve symptoms. Lidocaine (Answer B) would be best for initial treatment of the patient's neuropathic pain.

Sexual and Reproductive Health

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Sexual and Reproductive Health

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Learning Objectives

1. Recommend appropriate treatment options for patients with menopausal symptoms and osteoporosis.
2. Identify drugs that are considered safe and unsafe during pregnancy and lactation, through use of appropriate resources for pregnancy and lactation.
3. Select the appropriate treatment for infertility or sexual dysfunction on the basis of patient-specific factors.
4. Devise a pharmacotherapeutic plan for appropriate contraceptive use, including assessment of estrogen- and progestin-related adverse effects or drug interactions, contraceptive method mishaps, and use of emergency contraception.
5. Recommend appropriate pharmacotherapy for the treatment of pregnancy-related conditions and complications, menstrual disorders and sexually transmitted infections.

Abbreviations in This Chapter

ACE	Angiotensin-converting enzyme
aPTT	Activated partial thromboplastin time
BMD	Bone mineral density
BUM	Backup method
CHD	Coronary heart disease
COC	Combined oral contraceptive
CYP	Cytochrome P450
CVD	Cardiovascular disease
DMPA	Depot medroxyprogesterone acetate
DVT	Deep venous thrombosis
DXA	Dual-energy x-ray absorptiometry
EC	Emergency contraception
EPT	Estrogen and progestogen therapy
ET	Estrogen only therapy
FRAX	Fracture Risk Assessment Tool
FSH	Follicle-stimulating hormone
GnRH	Gonadotropin-releasing hormone
GSM	Genitourinary syndrome of menopause
hCG	Human chorionic gonadotropin
HSV	Herpes Simplex Virus
HT	Hormone therapy
IUD	Intrauterine device
IUS	Intrauterine system
LARC	Long-acting reversible contraception
LH	Luteinizing hormone
NSAID	Nonsteroidal anti-inflammatory drug
OTC	Over the counter
PCOS	Polycystic ovary syndrome
PDE	Phosphodiesterase
PID	Pelvic inflammatory disease
POP	Progestin-only pill/minipill
VTE	Venous thromboembolism

Self-Assessment Questions

Answers and explanations to these questions can be found at the end of this chapter.

1. M.T. is a 72-year-old white man (height 69 inches, weight 68 kg) with a history of hypertension who admits smoking one pack of cigarettes per day and having a poor diet. He states that he walks on his treadmill 30 minutes a day. His bone mineral density (BMD) T-score is –2.1 at the hip and –2.2 at the spine. His fracture history includes a fall at age 68 with an ankle fracture. His Fracture Risk Assessment Tool (FRAX) score (10-year major fracture probability) is 14%, and his probability of hip fracture is 6.7%. Which best describes M.T.'s condition?
   A. He has low bone mass (osteopenia) of the hip and spine.
   B. He has osteoporosis of the spine and low bone mass (osteopenia) of the hip.
   C. He has osteoporosis of the hip and spine.
   D. He has normal BMD of the hip and spine.

2. Which treatment is best for M.T.?
   A. Take calcium 1200 mg orally daily, vitamin D 800 international units orally daily, and alendronate 70 mg orally weekly.
   B. Take calcium 1200 mg orally daily and vitamin D 600 international units orally daily, and begin weight-bearing exercise.
   C. Take calcium 1200 mg orally daily, vitamin D 600 international units orally daily, and raloxifene 60 mg orally daily.
   D. Take calcium 1200 mg orally daily, vitamin D 400 international units orally daily, and risedronate 35 mg orally weekly, and begin weight-bearing exercise.

3. A 29-year-old woman (height 65 inches, weight 63 kg) has a history of two deep venous thromboses (DVTs) but is otherwise healthy; she is seeking to become pregnant. She currently takes warfarin 3 mg orally daily. Which regimen is the best recommendation for this patient?

A. Continue current warfarin dose to prevent clots during pregnancy.

B. Continue warfarin therapy but increase the dose to prevent clots during pregnancy.

C. Discontinue warfarin; start enoxaparin 60 mg subcutaneously every 12 hours until pregnant and continue through pregnancy.

D. Discontinue warfarin; start heparin 5000 units subcutaneously every 8 hours daily until 12 weeks pregnant, and then reinitiate warfarin.

4. J.K. is a 51-year-old postmenopausal woman with severe hot flashes that have not resolved with venlafaxine 75 mg orally daily. She is otherwise healthy, with no history of cancer and no surgical procedures. She is given conjugated estrogen 0.625 mg orally daily. Which treatment is best for J.K.?

A. No other drug is needed; estrogen alone is sufficient for hot flashes.

B. No other drug is needed; estrogen should be discontinued, and she should continue on venlafaxine.

C. Venlafaxine should be continued and medroxyprogesterone acetate should be added to decrease the risk of stroke.

D. Venlafaxine should be discontinued and medroxyprogesterone acetate should be added to decrease the risk of endometrial cancer.

5. C.S. is a 49-year-old postmenopausal woman experiencing severe hot flashes, vaginal dryness, and pain during sexual intercourse. C.S. has a history of irregular heavy uterine bleeding, which resulted in a total hysterectomy 5 months ago. Her hot flashes are affecting her quality of life. Which treatment is best to recommend for C.S.?

A. Estradiol vaginal cream 0.1 mg/g.

B. Conjugated estrogen and medroxyprogesterone acetate 0.625 mg/2.5 mg tablets.

C. Conjugated estrogen 0.3-mg tablets.

D. Ospemifene 60-mg tablets.

6. S.F. is a 20-year-old woman initiated on ethinyl estradiol 30 mcg/drospirenone 3 mg oral tablets 5 months ago for contraception. She was recently prescribed lamotrigine for bipolar disorder. Which best describes the drug interaction that may occur with ethinyl estradiol/drospirenone and lamotrigine in this patient?

A. The effectiveness of ethinyl estradiol and drospirenone may be decreased.

B. The effectiveness of lamotrigine may be increased.

C. The effectiveness of lamotrigine may be decreased.

D. The effectiveness of ethinyl estradiol and drospirenone may be increased.

7. A study compares the incidence of herpes simplex genital infections in patients receiving suppressive therapy with acyclovir versus valacyclovir. After 1 year of follow-up, 25% in the acyclovir group and 20% in the valacyclovir group experience a recurrent infection ($p<0.05$). Which best represents how many patients (in 1 year) would need to be treated with valacyclovir over acyclovir to prevent one recurrent infection?

A. 5.

B. 20.

C. 25.

D. There is insufficient information to calculate this number.

8. K.M. is a 28-year-old woman (height 68 inches, weight 98 kg) with a history of migraine with aura who is seeking contraception. Her blood pressure today is 135/82 mm Hg; she denies smoking and alcohol use and states that she would like to have children in a year or so. Which is the best contraceptive agent for K.M.?

A. Levonorgestrel intrauterine device (IUD).

B. Oral norethindrone tablet.

C. Transdermal ethinyl estradiol/etonogestrel patch.

D. Oral ethinyl estradiol/desogestrel tablet.

9. L.L. is a 38-year-old woman who has been trying to conceive for the past 7 months. Her husband's medical examination is normal; L.L. is not ovulating every month. She has not tried any medications previously to induce ovulation. Which medication is best to initiate in L.L. to induce ovulation?
   A. Human chorionic gonadotropin (hCG).
   B. Gonadotropin-releasing hormone (GnRH) agonist.
   C. Human menopausal gonadotropin (hMG).
   D. Clomiphene.

10. T.G. is a 22-year-old woman who comes to a community pharmacy and asks about emergency contraception (EC). She was swimming when her contraceptive vaginal ring slipped out. She has been without the ring for 3 days because she did not have a new one with her for replacement. She states she had unprotected intercourse 4 nights ago. She is worried about becoming pregnant. Which is the best recommendation for T.G.?
   A. Recommend that she see her physician for a levonorgestrel 1.5 mg prescription.
   B. Recommend EC; it may still be effective because she is within the 120-hour time window.
   C. Do not recommend EC; it may be ineffective because she is beyond the 72-hour time window.
   D. Do not recommend EC; instead, recommend that she insert a new contraceptive vaginal ring.

11. K.S. is a 45-year-old man who has difficulty maintaining an erection during intercourse. His medical history includes diabetes and hyperlipidemia. His drugs include aspirin, metformin, and pravastatin. Blood pressure is 130/81 mm Hg, hemoglobin A1C 6.2, total cholesterol 195 mg/dL, low-density lipoprotein cholesterol (LDL) 106 mg/dL, high-density lipoprotein cholesterol (HDL) 54 mg/dL, triglycerides 145 mg/dL, total testosterone concentration 970 ng/dL (reference range 270–1070 ng/dL), and free testosterone concentration 22 ng/dL (reference range 9–30 ng/ dL). Which drug is best to initiate for his erectile dysfunction?
   A. Vardenafil.
   B. Testosterone transdermal patch.
   C. Yohimbine.
   D. Fluoxetine.

12. T.M., a 33-year-old man, has a history of intravenous drug abuse and lives in and out of homeless shelters. He is taken to the emergency department by ambulance after experiencing paralysis on the right side of his body. The people at the shelter thought he might be having a stroke. In the emergency department, screening was positive for the Venereal Disease Research Laboratory test (syphilis test) with 10 white blood cells/mm^3. T.M. has no known significant medical history (except for treatment of a sexually transmitted disease [STD]), but he is allergic to penicillin (anaphylactic reaction). Assuming serologic testing confirms a diagnosis of syphilis, which therapy is best for T.M.?
   A. Levofloxacin 750 mg intravenously for one dose.
   B. Penicillin G 4 million units every 4 hours intravenously for 14 days after penicillin desensitization.
   C. Benzathine penicillin G 2.4 million units intramuscularly every week for 3 weeks after penicillin desensitization.
   D. Azithromycin 500 mg intravenously or orally daily for 6 weeks.

13. A prospective double-blind study compared the effects of three different antivirals—acyclovir, famciclovir, and valacyclovir—in 360 patients with first-episode genital herpes. Which statistical test is best to compare the mean duration of time until the lesions healed?
   A. Analysis of variance (ANOVA).
   B. Chi-square test.
   C. Mann-Whitney U test.
   D. Student t-test.

BPS Pharmacotherapy Specialty Examination Content Outline

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline, tested during the Spring 2024 window:

1. Patient-Centered Pharmacotherapy
   a. 1.1. Develop patient-centered, evidence-based pharmacotherapy plans. Subtasks: 1.1.1–1.1.17.
   b. 1.2. Monitor the patient to ensure safe and effective pharmacotherapy. Subtasks: 1.2.1–1.2.3.
   c. 1.3. Modify pharmacotherapy plans through ongoing patient assessment. Subtasks: 1.3.1–1.3.4, 1.3.7.
   d. 1.4. Communicate pharmacotherapy plans to patients, caregivers, and interprofessional team. Subtask: 1.4.1.
2. Application of Evidence to Practice and Education
   a. 2.1. Retrieve relevant information that addresses pharmacotherapy-related inquiries. Subtasks: 2.1.4, 2.1.6, 2.1.7.
3. Healthcare Systems and Population Health
   a. 3.1. Implement safe and effective medication use systems to improve healthcare system and population-based outcomes. Subtask: 3.1.2.
   b. 3.2. Utilize technology to promote safe and effective medication use. Subtasks: 3.2.1–3.2.3.
   c. 3.3. Incorporate public health initiatives to improve population health. Subtask: 3.3.2.

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline, tested starting Fall 2024:

1. Patient Care Specialty Areas
   a. 1A. Primary Pharmacotherapy Specialty Areas. Subtask: 1A4.
   b. 1C. Tertiary Pharmacotherapy Specialty Areas. Subtask: 1C3.
2. Therapeutics and Patient Management
   a. 2A. Treatment Planning. Subtasks: 2A1–2A6.
   b. 2B. Therapeutic Implementation. Subtasks: 2B1–2B3, 2B5.
   c. 2C. Treatment Outcomes and Monitoring. Subtasks: 2C1–2C5.

DISCLAIMER

This chapter covers topics that pertain to contraception, pregnancy, and lactation. Although this chapter has been updated with gender-neutral language to promote inclusivity, there may be instances that refer to pregnancy-capable people as women and mothers and instances that refer to lactation as nursing or breastfeeding.

Should this language persist whether intentionally (retaining original language used in referenced articles) or in error, a common understanding should be applied that these references and actions are related to individuals assigned female at birth and are not a commentary on gender identity.

I. HORMONE THERAPY AND MENOPAUSE

A. Background of Menopause
   1. Definition: Cessation of menstrual periods for 1 year, also known as final menstrual period, loss of ovarian follicular function
   2. Average age of menopause is 52 years, but ranges from 40 to 58 years.
   3. Common symptoms
      a. Vasomotor symptoms (hot flashes)
         i. Most common reason for treatment because they may impact quality of life. Common symptoms include increased skin temperature, nausea, dizziness, headache, palpitations, diaphoresis, and night sweats.
         ii. May interrupt sleep and cause insomnia
         iii. Occur in 75%–85% of people, usually within 12–24 months after the last menstrual period.
      b. Genitourinary syndrome of menopause (GSM): This syndrome includes genital symptoms of dryness, burning, and irritation; urinary symptoms and conditions of dysuria, urgency, and recurrent urinary tract infections (UTIs); and sexual symptoms of pain and dryness (Menopause 2020; 27:976-92).
         i. Decrease in estrogen and other sex steroids causes thinning of hair in the mons region and shrinkage of the labia minora; vulvovaginal atrophy (VVA) leads to pruritus and pain.
         ii. Loss of lubrication leads to dyspareunia (pain during sexual intercourse).
         iii. Vaginal pH changes and becomes more basic (from 4.5−5 to 6−8), creating a favorable environment for bacterial colonization.
         iv. Thinning of urethra and bladder lining and decreased muscle tone result in recurrent episodes of urinary frequency, urgency with dysuria, and urinary tract infections.

B. Treatments
   1. Individualization of therapy is essential. The patient's medical history must be considered, including cancer (specifically breast cancer), cardiovascular disease (CVD), stroke, hypertension, and quality of life with menopausal symptoms.
   2. *Hormone therapy* (HT) is an all-encompassing term that includes estrogen and progestogen therapy (EPT), estrogen-only therapy (ET), progestogen-only therapy (PT), and estrogen-receptor (ER) agonists or antagonists. (*Progestogen* is an umbrella term for progesterone [natural] and progestins [synthetic])
      a. FDA approved indications for HT: Treatment of moderate to severe vasomotor symptoms, treatment of moderate to severe GSM, prevention of postmenopausal osteoporosis, hypoestrogenism caused by hypogonadism, castration or premature ovarian failure.

b. Recommendations for HT
   i. Menopausal symptom relief
      (a) Moderate to severe vasomotor symptoms (primary indication)
         1. Recommend lowest effective dose.
         2. For patients younger than 60 or who are within 10 years of menopause onset without contraindications or at a high risk of CVD or breast cancer, assess the baseline risk of breast cancer and CVD, and consider risk when making a recommendation.
      (b) Moderate-to-severe GSM
         1. Vaginal symptoms – Recommend local ET versus systemic therapy if treating vaginal symptoms only
         2. Urinary health – Systemic HT may worsen stress incontinence; local ET therapy may help with overactive bladder
      (c) Sexual symptoms – HT not recommended for sole treatment of diminished libido
      (d) Osteoporosis – EPT and ET indication for prevention, ↓ osteoporotic fractures, used only when alternative therapies are not appropriate; ER agonists/antagonists may also be used for osteoporosis. See section below.

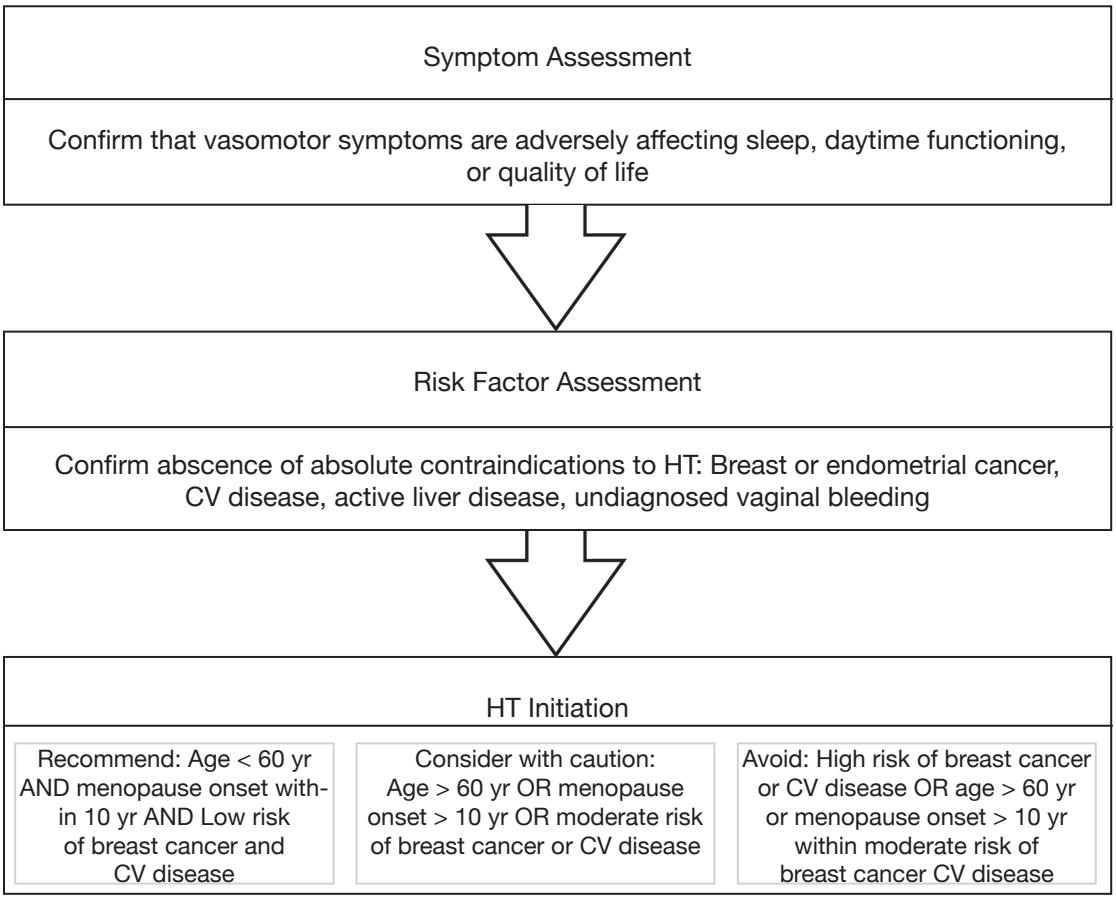


Figure 1. Risk Assessment for Initiating Hormone Therapy

CV = cardiovascular; HT = hormone therapy

Adapted from: Shifren JL, Crandall CJ, Manson JE. Menopausal hormone therapy. JAMA 2019;321:2458-9.

ii. Risk assessment (J Clin Endocrinol Metab 2015;100:3975-4011)
  (a) High risk of venous thromboembolism (VTE): Nonoral route at lowest effective dose is recommended (if not contraindicated).
  (b) High risk or history of breast cancer: Nonhormonal treatment is recommended for symptom relief.
  (c) High risk of CVD (known myocardial infarction [MI], cerebrovascular disease, peripheral arterial disease, abdominal aortic aneurysm, diabetes, chronic kidney disease, and 10-year CVD risk greater than 10%): Nonhormonal treatment is recommended for symptom relief.
  (d) Moderate risk of CVD: Transdermal estradiol with appropriate use of progestogen (individualized) is recommended.

c. Benefits and risks of estrogen and progestogens
  i. Benefits of estrogen
    (a) Relieves genitourinary atrophy
    (b) Relieves vasomotor instability
    (c) Osteoporosis: Reduction in hip fractures by 25%; reduction in vertebral fractures by 50%. Estrogen reduces the rate of bone resorption but does not reverse bone loss.
    (d) May help improve sleep by decreasing hot flashes
  ii. Risks of estrogen
    (a) Adverse effects: Bloating, headache, breast tenderness (5%–10%)
    (b) Endometrial cancer: Risk increases with unopposed estrogen use in women with an intact uterus.
      (1) Cancer risk increases 8-fold for 10–20 years of estrogen use.
      (2) Not recommended for use in people with a history of endometrial cancer. Patients with early stage, low-risk endometrial cancers (grade 1 and 2 endometrioid subtypes with negative estrogen and progesterone receptors) who used HT may have similar recurrence and death rates but overall recommendation is to avoid HT use in those with endometrial cancer, especially advanced stages (Menopause 2017;24:1-26).
      (3) A progestogen is recommended in all people with an intact uterus using estrogen (JAMA 1996;275:370-5, Menopause 2017;24:1-26).
    (c) Breast cancer with unopposed estrogen: Uncertain
      (1) The Women's Health Initiative (WHI) showed no increased risk and a nonsignificant decrease in risk in women who use estrogen for an average of 7.2 years. May increase relative risk among women who take estrogen for longer than 5 years, though some studies have not shown this risk (Menopause 2017;24:1-26).
      (2) Not recommended for use in women with a history of breast cancer (Menopause 2017;24:1-26).
      (3) Risk seems to increase with the addition of the progestogen and be related to the length of use. The risk is small and decreases after discontinuation of use.
    (d) Coronary heart disease (CHD): Possible increased risk of cardiovascular outcomes; not recommended for coronary protection at any age.
    (e) Gallbladder effects: oral estrogen may increase risk of gallbladder disease (gallstones, cholecystitis, cholecystectomy). Risk is slightly lower with medroxyprogesterone acetate in combination with estrogen (Menopause 2017;24:1-26).
  iii. Benefits of progestogen:
    (a) Decreased risk of estrogen-induced irregular bleeding
    (b) Decreased risk of endometrial hyperplasia and carcinoma

iv. Risks of progestogen
  (a) Adverse effects: Bloating, weight gain, irritability, depression (dose related)
  (b) Unpredictable endometrial bleeding with continuous estrogen/progestin during first 8–12 months (30%–50%)

v. Selected outcomes related to EPT and ET
  (a) Cardiovascular outcomes with conjugated estrogens and medroxyprogesterone acetate (JAMA 1998;280:605-13)
    (1) A longer duration of use leads to a greater decrease in relative hazards in nonfatal MI and CHD death; however, there was an increased risk of VTE and gallbladder disease.
    (2) Conclusions of study: HT was not appropriate to initiate for secondary prevention of CHD, but for patients already using HT, long-term use might result in a decrease in CHD.
    (3) A follow-up study suggested that older women with CHD who used HT for longer than 6.8 years had a higher risk of VTE and biliary tract surgery (JAMA 2002;288:58-66).
  (b) Other findings related to cardiovascular outcomes from various trials
    (1) Venous thromboembolism
      (A) Observational studies indicated increased risk.
      (B) A randomized controlled trial, the WHI (JAMA 2002;288:321-33), found increased risk in the EPT arm (18 additional VTEs per 10,000 women per year of EPT) and in the estrogen only therapy (ET) arm (7 additional VTEs per 10,000 women per year of ET).
      (C) In WHI, when EPT and ET were initiated in women 50–59 years of age, the risk of VTE was lower in this age group (11 additional VTEs per 10,000 women per year of EPT and 4 additional VTEs per 10,000 women per year of ET).
    (2) Stroke
      (A) Both EPT and ET showed an increased risk of stroke (8 additional strokes per 10,000 women per year of EPT and 11 additional strokes per 10,000 women per year of ET).
      (B) Women 50–59 years of age had no significant increase in stroke with EPT in the WHI, but in the ET group alone, risk doubled. Nurses' Health Study showed similar results (Cochrane Database Syst Rev 2015;3:CD002229).
    (3) Coronary heart disease
      (A) Observational studies indicated therapy may decrease CHD risk, but most women were younger than 55 and had entered menopause within the past 2–3 years.
      (B) Randomized controlled trials indicated an increased risk of CHD, but women had an average age of 63–64 years and had entered menopause about 10 years earlier. When adjusted for age, the estrogen-only arm of the WHI trial matches observational data, indicating a lower risk of CHD in younger patients.
      (C) Data show women who begin HT within 10 years of entering menopause may have a lower risk of CHD, whereas older women (more than 10 years from the onset of menopause) may have a higher risk of CHD.
      (D) Coronary artery calcium, a marker associated with atheromatous plaque burden and CHD risk, has been decreased in some observational studies. In the WHI study, estrogen-only arm participants had lower concentrations of coronary artery calcium after 7 years of treatment.

(E) Subclinical atherosclerosis, measured as carotid intima-media thickness, is reduced in women who started estrogen therapy with or without a progestogen less than 6 years past the time of menopause compared with placebo. This was not true in those who started hormone therapy 10 years or more after menopause onset (N Engl J Med 2016;374:1221-31).

(F) WHI findings (JAMA 2002;288:321-33). The WHI trial included conjugated estrogens and medroxyprogesterone acetate in healthy participants 50–79 years of age for primary prevention of CHD. Controversy exists because the average age of participants was older; thus, increases in breast cancer or CVD could be caused by age (Table 1).

Table 1. Summary of WHI Outcomes for EPT Use

Risk or Benefit	Relative Risk	Absolute Risk Each Year
Blood clots	2.11, or 111% ↑	18 more cases in 10,000 women
Dementia[a]	2.05, or 105% ↑	23 more cases in 10,000 women > 65
Strokes	1.41, or 41% ↑	8 more cases in 10,000 women
Heart attacks	1.29, or 29% ↑	7 more cases in 10,000 women
Breast cancer	1.26, or 26% ↑	8 more cases in 10,000 women
Hip fractures	0.66, or 33% ↓	5 fewer cases in 10,000 women
Colon cancer	0.63, or 37% ↓	6 fewer cases in 10,000 women

[a]Women's Health Initiative Memory Study.
EPT = estrogen and progestogen therapy; WHI = Women's Health Initiative.

(c) Further information suggests increased risk of ovarian cancer (data conflicting); long-term use greater than 5 years may increase risk, particularly in estrogen-only therapy; overall risk of occurrence considered rare, according to WHI data (JAMA 2009;302:298-305). A more recent meta-analysis showed that hormone therapy, regardless of type or regimen, was associated with an increased risk of ovarian cancer (Menopause 2016;4:417-24, Menopause 2017;24:1-26).

(d) Lung cancer may be increased in older women with a history of smoking (Lancet 2009;374:1243-51); some data are conflicting. Seems to be more associated with EPT use than with ET use.

(e) Cumulative 18-year follow-up on WHI trials of conjugated equine estrogens (0.625 mg/day) and medroxyprogesterone acetate (2.5mg/day) used for a median of 5.6 years or conjugated equine estrogens alone for a median of 7.2 years showed no difference in all-cause and cause-specific mortality risk (JAMA 2017;318:927-38).

vi. Formulations

(a) Oral: Used for vasomotor symptoms, also covers GSM if concomitant.

(b) Transdermal: Intolerant of oral preparations, used for vasomotor symptoms, also covers GSM if concomitant; consider as first-line for women with moderate risk of CVD if estrogen is needed.

(c) Vaginal and local preparations: For GSM. In general, topical treatment is sufficient and should be tried before oral preparations for patients experiencing no other symptoms.

vii. Hormone regimens
  (a) Therapy duration: Lowest dose for least amount of time. Check after 3 months to 1 year, and try to discontinue if asymptomatic; if symptoms recur, treat for an additional 3 months; best to limit treatment to less than 5 years.
  (b) Unopposed estrogen
    (1) People with a uterus must use estrogen in combination with progestogen; use of estrogen alone in people with a uterus causes endometrial hypertrophy and increases the risk of endometrial cancer (JAMA 1996;275:370-5).
    (2) Estrogen taken daily without interruption is suggested for those with a hysterectomy.
      (A) Transdermal estradiol patches can be used if intolerant of oral preparations or want nondaily administration
  (c) Estrogen plus cyclic progestogen
    (1) Continuous estrogen daily
    (2) Cyclic progestogen such as medroxyprogesterone acetate 5−10 mg/day for 10–14 days/month
    (3) Similar to female cycle, with a withdrawal bleed each cycle
  (d) Estrogen plus continuous progestogen
    (1) Continuous estrogen daily
    (2) Continuous progestogen such as medroxyprogesterone acetate 1.5–2.5 mg/day without interruption
    (3) Irregular menstrual cycle for the first 8–12 months of therapy, leading to amenorrhea
  (e) Intermittent
    (1) Continuous estrogen daily
    (2) Three days on progestogen, 3 days off
    (3) Seldom used

viii. Monitoring criteria
  (a) Monthly: Breast self-examination
  (b) Annually: Breast examination by provider, mammography, pelvic examination
  (c) Evaluation of potentially abnormal vaginal bleeding
    (1) Unopposed estrogen: Any episode of vaginal bleeding unless the person has had a health assessment deemed normal in the past 6 months
    (2) Estrogen plus cyclic progestogen: If bleeding occurs other than at the time of expected withdrawal bleeding
    (3) Estrogen plus continuous progestogen: If bleeding is heavier than normal, is prolonged (longer than 10 days at a time), is frequent (more often than monthly), or persists for more than 10 months after beginning therapy

ix. Products and dosing (Tables 2, 3, 4, 5, and 6)

Table 2. Oral Estrogen Products

Brand Name	Generic Name	Strengths (mg)
Estrace	17β-Estradiol	0.5, 1, 2
Femtrace	Estradiol acetate	0.45, 0.9, 1.8
Menest	Esterified estrogens	0.3, 0.625, 1.25
Premarin, Cenestin, Enjuvia	Conjugated estrogens	0.3, 0.45, 0.625, 0.9, 1.25

Table 3. Vaginal Estrogen Products

Formulation	Brand Name	Generic Name and Strength	Dose
Vaginal creams	Estrace	Micronized estradiol (0.1 mg/g)	Initial: 2–4 g/day for 1–2 wk; then gradually reduced to half the initial dose for 1–2 wk, followed by maintenance of 1 g/day applied vaginally one to three times weekly
	Premarin	Conjugated estrogens (0.625 mg/g)	Atrophic vaginitis: Use 0.5–2 g/day applied vaginally for 21 days and then 7 days off; may also use twice-weekly regimen of 0.5 g intravaginally for dyspareunia
Vaginal rings	Estring	17β-Estradiol (2-mg ring that delivers 7.5 mcg/day)	1 ring every 3 mo inserted vaginally
	Femring	Estradiol acetate (0.05 or 0.1 mg/day)	
Vaginal tablet	Vagifem, Yuvafem	Estradiol hemihydrate (10 mcg/day)	1 vaginal tablet once daily for 2 wk; then 1 tablet twice weekly
	Imvexxy	Estradiol inserts (4 or 10 mcg)	1 vaginal insert daily for 2 wk; then 1 vaginal insert twice weekly

Table 4. Transdermal Estrogen Products

Brand Name	Formulation	Estrogen Provided (mg/day)	Dose	Unique Traits and Counseling Points
Alora	17β-Estradiol matrix patch	0.025, 0.05, 0.075, 0.1	1 patch twice weekly	Rotate sites of application to avoid irritation for all patches Minivelle should be placed on dry skin below umbilicus on abdomen or buttocks Menostar is lowest-dose transdermal patch available; indicated only for prevention of postmenopausal osteoporosis
Climara		0.025, 0.0375, 0.05, 0.06, 0.075, 0.1	1 patch weekly	
Minivelle		0.025, 0.0375, 0.05, 0.075, 0.1	1 patch twice weekly	
Vivelle-Dot, Dotti		0.025, 0.0375, 0.05, 0.075, 0.1	1 patch twice weekly	
Menostar		0.014	1 patch weekly	
Lyllana		0.025, 0.0375, 0.05, 0.075, 0.1	1 patch twice weekly	
Estraderm		0.05, 0.1	1 patch twice weekly	
Divigel 0.1%	17β-Estradiol transdermal gel	Unknown	0.25, 0.5, 0.75, or 1 g of gel	Apply Divigel to one leg daily, alternate sites daily
Elestrin 0.06%		0.52 (0.0125 absorbed), 1.04 (0.0375 absorbed)	0.25, 0.5, 0.75, or 1 g of gel	Apply Divigel to one leg daily, alternate sites daily
EstroGel 0.06%		0.75 (0.035 absorbed)	0.25, 0.5, 0.75, or 1 g of gel	Apply Divigel to one leg daily, alternate sites daily
Evamist	17β-Estradiol transdermal spray	1.53 (0.021 absorbed)	Initial 1 spray/day (1.53 mg) increasing to 2 or 3 sprays/day	1 spray on forearm daily, can increase to 2 or 3 sprays on forearm daily

Table 5. Combination Products

Brand Name	Generic Name	Hormone Strengths	Dose
Activella, Amabelz, Mimvey, Lopreeza	17β-Estradiol/ norethindrone acetate	0.5 mg estrogen, 0.1 mg norethindrone (Mimvey unavailable at 0.5/0.1 mg strength); 1 mg estrogen, 0.5 mg norethindrone	1 tablet daily
Angeliq	17β-Estradiol/ drospirenone	1 mg estrogen, 0.5 mg drospirenone; 0.5 mg estrogen, 0.25 mg drospirenone	1 tablet daily
Climara Pro	17β-Estradiol/ levonorgestrel	0.045 mg estrogen, 0.015 mg levonorgestrel	1 patch weekly
CombiPatch	17β-Estradiol/ norethindrone acetate	0.05 mg estrogen, 0.14 mg norethindrone 0.05 mg estrogen, 0.25 mg norethindrone	1 patch twice weekly
Bijuva	17β-Estradiol/ progesterone	1 mg estrogen, 100 mg progesterone	1 capsule every evening with food
Jinteli, Fyavolv	Ethinyl estradiol/ norethindrone acetate	0.0025 mg estrogen, 0.5 mg progestogen (Fyavolv) 0.005 mg estrogen, 1 mg norethindrone	1 tablet daily
Prefest	17β-Estradiol/ norgestimate	1 mg estrogen, 0.09 mg norgestimate	3 days of estrogen tablets only, 3 days of estrogen and progestogen
Premphase	Conjugated estrogens/ medroxyprogesterone acetate	0.625 mg estrogen, 5 mg medroxyprogesterone	0.625 mg/day for 14 days; then 0.625 mg and 5 mg/day for 14 days
Prempro	Conjugated estrogens/ medroxyprogesterone acetate	0.3 mg estrogen, 1.5 mg medroxyprogesterone; 0.45 mg estrogen, 1.5 mg medroxyprogesterone; 0.625 mg estrogen, 2.5 mg medroxyprogesterone	1 tablet daily

Table 6. Progestogen Products

Brand Name	Generic Name	Dosage Strengths and Formulation
Crinone 4%, 8%	Progesterone gel	45-mg vaginal applicator vaginally, 90-mg vaginal applicator vaginally
Endometrin	Progesterone vaginal suppository	100 mg vaginal suppository
Prometrium	Micronized progesterone in peanut oil	100- and 200-mg oral capsules
Provera	Medroxyprogesterone acetate	2.5-, 5-, and 10-mg oral tablets

d. Selective estrogen receptor modulators, also known as estrogen receptor agonist/antagonists, indicated for use in menopause symptoms. Benefits include provision of endometrial protection in patients with a uterus, without the need for a progestogen.
   i. Ospemifene 60-mg oral tablets (Osphena): 1 tablet orally daily
      (a) Indicated for the treatment of moderate to severe dyspareunia or vaginal dryness caused by vulvar and vaginal atrophy of menopause.
      (b) Agonist on endometrial lining affects uterine endometrium; it is recommended that people with a uterus add a progestin to any agent with estrogenic properties, although clinical studies with ospemifene alone did not find an increased risk of endometrial hyperplasia. No studies are available evaluating the use of ospemifene with a progestin.

(c) Adverse reactions (greater than 1%)
(1) Hot flashes
(2) Muscle cramps
(3) Vaginal discharge
(4) Hyperhidrosis
(d) Contraindications similar to those of estrogen (e.g., history of estrogen-dependent cancer, undiagnosed vaginal bleeding)
(1) Pregnancy, nursing, pediatrics
(2) History of VTE
(3) Severe hepatic impairment (Child-Pugh class C)
(e) Drug interactions
(1) Rifampin decreases ospemifene exposure by 59%. Avoid concomitant use.
(2) Fluconazole increases ospemifene concentrations 2.7-fold and should not be used concomitantly; ketoconazole increases ospemifene 1.4-fold.
(3) Highly protein bound, about 99%; may affect other medications that are protein bound.
(4) Should not be given with estrogen products, including other selective estrogen receptor modulators.

ii. Conjugated estrogens 0.45 mg plus bazedoxifene 20 mg oral tablets (Duavee); 1 tablet orally daily (see Osteoporosis section in text that follows for more information)
(a) Indicated for treatment of moderate to severe vasomotor symptoms and prevention of osteoporosis in patients with a uterus.
(b) Selective estrogen receptor modulator used instead of a progestin
(c) May increase risk of DVT; should not be used with a history of blood clots; has contraindications similar to those of estrogen.
(d) Common adverse effects: Muscle spasms; nausea and vomiting; throat, neck, or upper abdominal pain; and indigestion

e. Fezolinetant (Veozah)
i. Mechanism of action: Neurokinin 3 receptor antagonist that restores normal state of thermoregulatory system
ii. Indicated for moderate to severe vasomotor symptoms as an alternative to HT
iii. Dosing: 45 mg orally daily
iv. Common adverse events: Abdominal pain, diarrhea, insomnia, back pain, hot flashes
v. Monitoring: Liver function tests at baseline and every 3 months for the first year
vi. Interactions: CYP1A2 inhibitors

f. Prasterone vaginal insert (Intrarosa)
i. Indicated for the treatment of moderate to severe dyspareunia due to vulvar and vaginal atrophy resulting from menopause.
ii. Inactive endogenous steroid that is converted into androgens and/or estrogens. Mechanism of action is not fully understood.
iii. Administration: Prasterone 6.5 mg placed vaginally once at bedtime
iv. Should not be used with current or past history of breast cancer; contraindicated in undiagnosed genital bleeding.
v. Common adverse effects: Vaginal discharge and abnormal pap smear
vi. May be stored in refrigerator or at room temperature.

g. Other hormone products
i. Bioidentical hormones: May still have adverse effects similar to those of conjugated/esterified estrogens and synthetic progestins.
ii. Androgens: Testosterone may help with sexual dysfunction but not vasomotor symptoms; not approved for use.

iii. Phytoestrogens (see text that follows for soy isoflavones): Act similarly to estrogen and carry similar contraindications.
iv. Megestrol (progestogen; see earlier section on progestogens)

3. Serotonin reuptake inhibitors: Best for vasomotor symptoms in high-risk people for whom HT is not recommended.
   a. Paroxetine 7.5 mg orally once daily (Brisdelle; only selective serotonin reuptake inhibitor with indication for vasomotor symptoms)
   b. Venlafaxine 75 mg orally once daily
   c. Fluoxetine 20 mg orally once daily
   d. Paroxetine 20 mg orally once daily
   e. Sertraline 100 mg orally once daily
   f. Escitalopram 10–20 mg orally once daily
   g. Citalopram 10–20 mg orally once daily
   h. Desvenlafaxine 100–150 mg orally once daily
4. Natural products: Some data for effectiveness (no FDA indication)
   a. Soy isoflavones: May still have adverse effects similar to those of conjugated estrogens.
   b. Evening primrose oil: No solid evidence for use.
   c. Black cohosh: Some effectiveness for vasomotor symptoms; reports of liver toxicity.
5. Others: Used for vasomotor symptoms (no FDA indication) (Int J Womens Health 2012;4:305-19)
   a. Clonidine
   b. Gabapentin
   c. Pregabalin
   d. Acupuncture
   e. Hypnosis
   f. Lifestyle changes

Patient Case

1. A 56-year-old woman presents to her primary care provider with reports of increased urinary frequency and pain during sexual intercourse. These symptoms have increased since her last menstrual period, about 9 months ago. She denies any medical history significant for cancer. Which recommendation is most appropriate for her today?

   A. Estrace (micronized estradiol) 2–4 g vaginally per day.

   B. Climara (17β-estradiol) 0.05 mg patch transdermal once weekly.

   C. Lopreeza (17β-estradiol/norethindrone acetate) 0.5 mg/0.1 mg tablet orally daily.

   D. Premarin (conjugated estrogens) 0.3 mg tablet orally daily.

II. OSTEOPOROSIS

A. World Health Organization (WHO) Definitions Based on T-scores (T-score indicates that for every standard deviation [SD] below the mean young adult bone mineral density [BMD], fracture risk increases 2-fold)
   1. Normal = BMD within 1 SD of the young adult mean.
   2. Low bone mass (osteopenia) = BMD 1–2.5 SD below the young adult mean (often seen as T-score between -1 and -2.5).
   3. Osteoporosis = BMD at least 2.5 SD below the young adult mean (often seen as T-score less than –2.5).
   4. Severe or established osteoporosis = BMD 2.5 SD below the young adult mean (often seen as T-score less than -2.5) with a fragility fracture

B. Guidelines were updated by the North American Menopause Society (NAMS) in 2021 and by the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) in 2020 (Table 7). The American College of Physicians (ACP) released a focused update for osteoporosis treatment in 2023 to update the full guidelines from 2017. Additional guidelines that influence osteoporosis care include the 2019 Pharmacological Management of Osteoporosis in Postmenopausal Women: An Endocrine Society (ES) Clinical Guideline and Osteoporosis in Men.

Table 7. 2020 AACE/ACE Criteria for Diagnosis of Osteoporosis in Postmenopausal Women

T-score -2.5 or below (lumbar spine, femoral neck, total proximal femur, or 1/3 radius)
Low-trauma spine or hip fracture (regardless of bone mineral density)
T-score between -1.0 and -2.5 **and** a fragility fracture (proximal humerus, pelvis, distal forearm)
T-score between -1.0 and -2.5 **and** high FRAX fracture probability

FRAX = Fracture Risk Assessment Tool.

1. Risk factors for osteoporotic fractures
    a. Female sex
    b. White race
    c. Poor nutrition, long-term low-calorie intake
    d. Early menopause (before age 40-45 years) or prolonged premenopausal amenorrhea
    e. Estrogen deficiency
    f. Drugs: glucocorticoids, heparin, anticonvulsants, excessive levothyroxine, gonadotropin-releasing hormone (GnRH) agonists, lithium, cancer drugs, proton pump inhibitors, sodium glucose-like transporter-2 inhibitors, selective serotonin-reuptake inhibitors
    g. Low BMI or low weight
    h. Family history of osteoporosis
    i. Low calcium and vitamin D intake
    j. Sedentary lifestyle, decreased mobility
    k. Cigarette smoking
    l. Chronic alcohol use
    m. Dementia
    n. Impaired eyesight despite adequate correction
    o. Previous fractures
    p. History of falls
    q. Type 1 and Type 2 diabetes
    r. Inflammatory bowel disease
    s. Chronic liver disease
2. Recommendations
    a. Avoid smoking and consume only moderate amounts of alcohol.
    b. Regular weight-bearing and muscle-strengthening exercise.
    c. Adequate intake of calcium (at least 1000 mg/day) and vitamin D (800–1000 international units/day) according to the National Osteoporosis Foundation (NOF), or 600 international units/day for those younger than 70 years and 800 international units/day for 70 years or older according to the Institute of Medicine (IOM).
    d. Assessment
        i. Dual-energy x-ray absorptiometry (DXA): Gold standard, measures hip or lumbar spine BMD
        ii. Quantitative computed tomography (QCT): Measures volumetric BMD of lumbar spine
        iii. Peripheral DXA (pDXA) and peripheral QCT (pQCT): Not appropriate for monitoring

iv. Vertebral imaging: Used to identify vertebral fractures because they are often asymptomatic
  (a) All women 70 years or older and men 80 years or older with BMD T-score of –1.0 or less at spine, total hip, or femoral neck
  (b) Women 65–69 years and men 70–79 years if BMD T-score is –1.5 or less at spine, total hip, or femoral neck
  (c) Postmenopausal women or men 50 and older with the following risk factors:
    (1) Low-trauma fracture as an adult (age 50)
    (2) Historical height loss of 1.5 inches (4 cm) or more (since peak in adulthood)
    (3) Prospective height loss of 0.8 inches (2 cm) or more (measured at medical assessments)
    (4) Recent or ongoing long-term glucocorticoid treatment
  (d) Follow-up needed only if new back pain or further height loss is documented

v. Clinical screening tools
  (a) Fracture Risk Assessment Tool (FRAX) score items (www.sheffield.ac.uk/FRAX/tool.jsp)
    (1) Used to estimate fracture risk
    (2) Most useful to estimate for patients with low BMD of hip
    (3) Recommended for postmenopausal women and men 50 years or older
    (4) Useful to determine whether patients with low bone mass (osteopenia) need pharmacologic treatment
    (5) Not validated for patients on drug therapy for osteoporosis
    (6) No data to show benefit in fracture reduction based on use for treatment decisions.
  (b) Other screening tools
    (1) Simple Calculated Osteoporosis Risk Estimation (SCORE)
    (2) Osteoporosis Risk Assessment Instrument (ORAI)
    (3) Osteoporosis Index of Risk (OSIRIS)
    (4) Osteoporosis Self-Assessment Tool (OST)

e. Recommended BMD testing
  i. All women 65 years and older and men older than 70. The USPSTF recommends osteoporosis screening for the prevention of fractures for women but stated that evidence was insufficient for weighing the risk-benefit for screening in men (JAMA 2018;319:2521-31).
  ii. Men 50–69 years of age with previous fractures or risk factors such as delayed puberty, hypogonadism, hyperparathyroidism, hyperthyroidism, or chronic obstructive pulmonary disease; drugs such as glucocorticoids or GnRH agonists; alcohol abuse or smoking; or other causes of secondary osteoporosis
  iii. All postmenopausal women with medical causes of bone loss
  iv. Postmenopausal women younger than 65 years with at least one of the following:
    (a) Previous fracture after menopause other than skull, facial bone, ankle, finger, or toe; thinness (body weight less than 127 lb [58 kg] or BMI less than 21 kg/m^2); history of hip fracture in a parent; current smoking; rheumatoid arthritis, alcohol intake of 2 units/day or more (1 unit = 12 oz beer, 4 oz wine, 1 oz liquor)
    (b) With any risk factor listed in section B1
    (c) Previous fracture not caused by severe trauma after age 40–45
    (d) Thinness (body weight less than 127 lb [58 kg]), family history of spine or hip fracture
    (e) Low bone mass (osteopenia) identified radiographically
    (f) Starting or taking long-term systemic glucocorticoids for 3 months or longer (e.g., prednisolone 5 mg/day or equivalent dose).
    (g) When use of a clinical tool for screening (FRAX, SCORE, OST, ORAI, or OSIRIS) in women suggests BMD assessment is necessary (JAMA 2018;319:2521-31)

f. Initiation of drug therapy
   i. If hip or spine fracture
   ii. If BMD T-score is -2.5 or below at spine, hip, or femoral neck
   iii. If BMD T-score is between -1.0 and -2.5 at the femoral neck or spine and the FRAX 10-year probability of hip fracture is 3% or greater, or the FRAX 10-year probability of major osteoporosis-related fracture is 20% or greater
g. Length of drug therapy: American College of Physicians recommends 5 years of pharmacologic therapy for women with osteoporosis, NAMS recommends a bisphosphonate holiday only in those with low fracture risk who no longer meet criteria for therapy.
h. Recommendations for follow-up on BMD-DXA vary. The 2021 NAMS position statement suggests repeat BMD testing 1–2 years after beginning treatment or when considering a change in therapy. The 2020 AACE/ACE guidelines discuss using bone turnover markers (BTMs) (e.g., propeptide of type 1 collagen [P1NP] for bone formation; C-terminal telopeptide type 1 collagen [CTX] for bone resorption) to assess treatment adherence and efficacy. A recent fracture can cause a transient elevation in BTM. The interval may be longer in patients with T-scores in the normal or upper bone mass range who do not have major risk factors.

C. Osteoporosis Treatments
1. Bisphosphonates (Table 8)
   a. Inhibit normal and abnormal bone resorption
   b. First-line therapy (Ibandronate is considered second-line therapy)
   c. Efficacy: Reduces vertebral and non-vertebral fractures by 30%–50% (see individual agents; Ibandronate reduces only vertebral fractures)
   d. Adverse events (not dose-dependent)
      i. Gastrointestinal (GI): Flatulence, acid regurgitation, esophageal ulcer, dysphasia, abdominal distention, gastritis. To reduce the risk of GI adverse effects, avoid lying down for 30–60 minutes after taking the dose.
      ii. Miscellaneous: Headache, musculoskeletal pain, rash
      iii. Laboratory values: Decreases in serum calcium concentrations; decreases in serum phosphorus concentrations in the first month.
      iv. Osteonecrosis of jaw: Most are associated with dental procedures. Most cases occur in patients with cancer after prolonged therapy. High-dose intravenous administration (usually for cancer-related issues) has a greater risk than oral therapy.
      v. Atypical fractures: Potentially associated with longer duration of use; FDA recommends considering periodic reevaluation of continued need for therapy (FDA Drug Safety Communication, 2016)
      vi. Esophageal cancer: FDA is monitoring the conflicting data; recommendation is to continue use as directed by physician (FDA Drug Safety Communication, 2017)
      vii. Atrial fibrillation: Possible increased risk of atrial fibrillation but not of stroke or cardiovascular mortality (Chest 2013;144:1311-22). One meta-analysis showed no increased risk of stroke, myocardial infarction, total cardiovascular events or death (PLoS One 2015;10:e0122646).
   e. Drug holidays are controversial; bone density may decrease 5 years after discontinuation of bisphosphonate therapy, but risk of hip fracture stays the same; however, higher risk of vertebral fracture may occur.
      i. American Society for Bone and Mineral Research recommends that women be reassessed after 5 years of oral bisphosphonate use or 3 years of intravenous treatment.
      ii. Women at a high risk of fractures should continue oral therapy for up to 10 years and up to 6 years with intravenous therapy with intermittent follow-up (AACE/ACE).

iii. Women whose fracture risk decreased after 3–5 years of use should stop treatment for 2–3 years (J Bone Miner Res 2016;31:16-35).

f. Drug-food interactions: Wait at least 30 minutes after taking bisphosphonate before taking any medications, food, or drinks except for water. Exceptions: oral ibandronate (must wait 60 minutes), risedronate sodium, delayed release (must be taken with food.)

g. Administration considerations
   i. Alendronate (daily dose regimen): was shown to decrease vertebral fractures by 47% and hip fractures by 51% (Fracture Intervention Trial [FIT]) in women with previous fractures.
   ii. Alendronate 70-mg effervescent tablet/week (Binosto): Dissolve tablet in 4 oz water, wait for about 5 minutes for effervescence to stop, stir for 10 seconds, and drink contents. Has similar recommendations of waiting 30 minutes before eating or drinking and staying upright for 30 minutes after administration.
   iii. Risedronate: Decreases non-vertebral fracture risk by 33%–39% and vertebral fracture by 41%–49%
   iv. Ibandronate: wait at least 60 minutes before eating, drinking, or taking another drug. Increases BMD at spine and hip; however, studies show only a decreased risk of vertebral fractures.
   v. Zoledronic acid: infuse over a minimum of 15 minutes; reduces non-vertebral fracture risk by 25%, hip fracture by 40%, and vertebral fracture risk by 70%. Lack of GI adverse effects; higher risk of atrial fibrillation with zoledronic acid than with placebo (1.3% vs. 0.4%); hypocalcemia may occur; patient must take calcium and vitamin D supplements. Infusion reactions occur, necessitating pretreatment with acetaminophen. Shown to decrease mortality in high-risk patients who have had a hip fracture (only bisphosphonate shown to decrease mortality)

h. Dose adjustments may be necessary in renal impairment (see Table 8).

Table 8. Bisphosphonates

Drug	Indications	Osteoporosis Dosing and Routes
Alendronate (Fosamax, Binosto) Alendronate + cholecalciferol (Fosamax Plus D)	Prevention and treatment of osteoporosis in postmenopausal women, increase BMD in men, glucocorticoid-induced osteoporosis Paget disease	10 mg PO daily 70 mg PO weekly, 70-mg effervescent tablet PO weekly, 70 mg/75 mL solution PO weekly 70 mg PO weekly + cholecalciferol 2800 international units/wk or 5600 international units/wk 5 mg PO daily for prevention 35 mg PO weekly for prevention Not recommended for CrCl < 35 mL/min
Risedronate (Actonel) Risedronate delayed release (Atelvia)	Prevention and treatment of osteoporosis in postmenopausal women, increase BMD in men, glucocorticoid-induced osteoporosis Paget disease	5 mg PO daily 35 mg PO weekly (immediate and delayed release) 150 mg PO monthly Not recommended for CrCl < 30 mL/min

Table 8. Bisphosphonates (*Cont'd*)

Drug	Indications	Osteoporosis Dosing and Routes
Ibandronate (Boniva)	Prevention and treatment of osteoporosis in women	150 mg PO monthly 3 mg IV every 3 mo Not recommended for CrCl < 30 mL/min
Zoledronic acid (Reclast)	Prevention and treatment of osteoporosis in postmenopausal women, increase BMD in men, glucocorticoid-induced osteoporosis Paget disease	5 mg IV yearly 5 mg IV every 2 yr (prevention in women) Not recommended for CrCl < 35 mL/min

BMD = bone mineral density; CrCl = creatinine clearance; IV = intravenously; PO = by mouth.

2. Denosumab (Prolia): Approved for postmenopausal women with osteoporosis at high risk of fracture, for increasing bone mass in men with osteoporosis, for treatment of glucocorticoid-induced osteoporosis, and for men and women with bone loss associated with prostate or breast cancer.
    a. Inhibits osteoclast-mediated bone resorption; monoclonal antibody against receptor activator of nuclear factor κ β ligand (RANKL) (cytokine essential for formation, function, survival of osteoclasts)
    b. Considered alternative first-line therapy.
        i. Patients at high risk of fracture or intolerant of or unresponsive to bisphosphonates
        ii. Patients with impaired renal function
    c. Administered as 60 mg subcutaneously every 6 months
    d. Not contraindicated with renal dysfunction.
    e. Efficacy
        i. Increased hip (6%) and spine (9%) BMD
        ii. Reduced spinal fracture risk by 68%, hip fracture risk by 40%
        iii. Optimal duration is not well studied. Length of therapy guided by clinical judgment and re-evaluation of fracture risk.
    f. Safety issues
        i. Possible opportunistic infections, skin infections such as cellulitis
        ii. Hypocalcemia: Patients should take calcium and vitamin D together with denosumab. Those with impaired renal function are more likely to have hypocalcemia.
        iii. The FDA has Risk Evaluation and Mitigation Strategies (REMS) requirements for this drug (Medication Guide).
        iv. Administration of a bisphosphonate after denosumab discontinuation has been proposed as a strategy to mitigate a transient rebound of bone turnover causing rapid BMD loss and increased risk of multiple vertebral fractures (Osteoporos Int 2016;27:1677-82).
3. Calcium
    a. Recommended for all patients to maintain normal calcium concentrations and to prevent hypocalcemia associated with other drug treatments for osteoporosis
    b. Elemental calcium intake: Avoid doses higher than 2500 mg/day. Higher doses may increase risk of constipation, contribute to kidney stones, and inhibit absorption of zinc or iron (Table 9).
    c. Most common forms: Calcium carbonate (take with food), calcium citrate (take with or without food, may be good option for patients taking antacids or acid-suppressive therapy or for patients with achlorhydria)
    d. Systematic reviews and meta-analyses have raised concerns about the potential association between calcium supplements and an increased risk of cardiovascular disease (Nutrients 2021;13:368).

Table 9. Recommended Daily Calcium Intake

Age Group	Recommended Daily Calcium Intake (mg)
19–50 yr: Women 51–70 yr: Men	1000
≥ 51 yr: Women ≥ 71 yr: Men	1200

4. Vitamin D
    a. Recommended for all patients; promotes calcium reabsorption.
    b. Minimum dose is 800 international units/day for those older than 70 years, 600 international units/day age 70 years and younger.
    c. Higher doses of vitamin D may be necessary for those with vitamin D concentrations less than 30 ng/mL.
    d. Goal: 30 ng/mL in adults, although concentrations of 20 ng/mL may be adequate for most of the population.
5. Selective estrogen receptor modulators
    a. Raloxifene (Evista)
        i. Indication: Prevention and treatment of osteoporosis in postmenopausal women. Risk reduction for invasive breast cancer in postmenopausal women
        ii. Preferred agent in this class because of long-term safety/efficacy data and reduced risk of breast cancer
        iii. Mechanism: Selective estrogen receptor modulator
            (a) Reduction in resorption of bone.
            (b) Decrease in overall bone turnover.
            (c) Data suggest estrogen antagonist in uterine and breast tissue.
            (d) Consider use for primary prevention in women with low BMD and a 5-year risk of developing invasive breast cancer greater than 3% (Ann Intern Med 2013;158:604).
        iv. Efficacy
            (a) Reduces the risk of vertebral fractures (30%–50%); has not been shown to decrease hip fractures.
            (b) Lowers total cholesterol by 7% and LDL by 11%; does not reduce risk of CHD.
        v. Adverse reactions
            (a) Hot flashes: 6%–25%
            (b) Leg cramps: 6%
            (c) VTE: About 1% (2- to 3-fold increased risk compared with placebo)
        vi. Dose: 60 mg/day orally
        vii. Contraindications
            (a) Pregnancy, breast/chestfeeding, pediatrics
            (b) History of VTE events; greatest risk of VTE events occurs during first 4 months.
        viii. Drug interactions
            (a) Bile acid resins decrease absorption by 60%.
            (b) Warfarin: Prothrombin time is decreased by 10%.
            (c) Thyroid hormones: Separate administration by 12 hours.
    b. Conjugated estrogens and bazedoxifene (Duavee)
        i. Indication: Prevention of osteoporosis in postmenopausal women
        ii. Few long-term safety data. Considered alternative agent to prevent bone loss in patients with a uterus and persistent menopausal symptoms who cannot tolerate other drugs.

iii. Mechanism: Selective estrogen receptor modulator plus estrogen (tissue-selective estrogen complex [TSEC])
iv. Efficacy
(a) Significantly increased total hip BMD at 24 months by 1.96% compared with placebo in women who had been postmenopausal for 1–5 years and by 1.73% in women who had been postmenopausal for more than 5 years.
(b) Significantly increased mean lumbar spine BMD (by 1.51%) compared with placebo at 12 months in women who had been postmenopausal for 1–5 years.
v. Adverse reactions (5% or more)
(a) Hot flashes
(b) Muscle cramps
(c) Throat, neck, and muscle pain
(d) Dizziness
(e) Nausea and vomiting
vi. Dose: Conjugated estrogen 0.45 mg and bazedoxifene 20 mg/day orally
vii. Contraindications
(a) Pregnancy, breast/chestfeeding, pediatrics
(b) History of VTE events or coagulopathy
(c) Hepatic impairment
(d) Similar to estrogen contraindications
viii. Drug interactions: Metabolized by cytochrome P450 (CYP) 3A4; inducers or inhibitors of CYP3A4 may affect estrogen concentrations.

6. Human parathyroid hormone related peptide analogs
a. Teriparatide (Forteo)
i. Recombinant human parathyroid hormone regulates bone metabolism, intestinal calcium absorption, and renal tubular calcium and phosphate reabsorption.
ii. Indications: Treatment of postmenopausal women with osteoporosis that have a high risk of fracture, increase bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture
iii. Efficacy
(a) Reserved for treating women at high risk of fracture, including those with very low BMD (T-score lower than –3.0) and a previous vertebral fracture.
(b) Decreases vertebral fractures by 65% and non-vertebral fractures by 53%; not shown to decrease hip fractures.
iv. Contraindications: Hypercalcemia, bone metastases, disorders that predispose women to bone tumors such as Paget disease, and alkaline phosphatase elevation (unexplained)
v. Adverse effects: Nausea, orthostatic hypotension
vi. Carcinogenicity: Osteosarcoma in rats; should not be used longer than 2 years.
vii. Drug interactions: Increases calcium concentrations and may increase risk of digoxin toxicity.
viii. Dosage: 20 mcg/day subcutaneously
b. Abaloparatide (Tymlos)
i. Regulates bone metabolism, intestinal calcium absorption, and renal tubular calcium and phosphate reabsorption.
ii. Indication: Treatment of postmenopausal women with osteoporosis that have a high risk of fracture.

iii. Efficacy
(a) Reserved for treating women at high risk of fracture, including those with very low BMD (T-score lower than –3.0) and a previous vertebral fracture.
(b) Decreases vertebral fractures by 86% and non-vertebral fractures 43%; not shown to decrease hip fractures.
iv. Contraindications: None
v. Precautions (1) Orthostatic hypotension; (2) Hypercalcemia; (3) Hypercalciuria and urolithiasis:
vi. Adverse effects: Nausea, dizziness, headache, palpitations, hypercalciuria, upper abdominal pain, and vertigo
vii. Carcinogenicity: Osteosarcoma in rats; should not be used longer than 2 years.
viii. Drug interactions: Increases calcium concentration and may increase risk of digoxin toxicity.
ix. Dosage: 80 mcg/day subcutaneously; patients should also take supplemental calcium and vitamin D if dietary intake is not enough.

7. Romosozumab-aqqg (Evenity)
a. Sclerostin (a factor in bone regulation) inhibitor, helps build bone and decreases bone resorption.
b. Indication: Treatment of osteoporosis in postmenopausal women who are at high risk of fracture (defined as a history of osteoporotic fracture or several risk factors for fracture) or for those whose other osteoporosis treatments have failed
c. Efficacy: Decreased the absolute risk of new vertebral fracture by 1.3% at 12 months (fracture risk in placebo group 1.8% vs. 0.5% in treatment group, p<=0.001) and by 1.9% at 24 months (fracture risk in placebo group 2.5% vs. 0.6% in treatment group, p=<0.001); increased BMD by 12.7% at lumbar spine, 5.8% at total hip, 5.2% at femoral neck
d. Contraindications: Hypocalcemia, sensitivity to romosozumab
e. Precautions: Major adverse cardiac events (MI, stroke); hypocalcemia; hypersensitivity (e.g., allergic reaction, angioedema); osteonecrosis of the jaw and atypical femoral fracture
i. Should not be initiated in patients who have had an MI or stroke within the previous year.
ii. Consider risk-benefit of therapy in patients with other CV risk factors.
f. Adverse effects: Joint pain and headache
g. Carcinogenicity: None reported
h. Dosages: 210 mg injected subcutaneously once a month for 12 months. Requires 2 injections to achieve the dose of 210 mg (give one after the other). Patients should also take supplemental calcium and vitamin D if dietary intake is not enough. No dosage adjustments for renal impairment; however, in patients receiving dialysis or who have a creatinine clearance less than 29 mL/minute, may increase the risk of hypocalcemia

8. Calcitonin-salmon (Miacalcin)
a. Inhibition of bone resorption
b. Not first-line; reserved for short-term use for bone pain caused by vertebral compression fractures, no longer used frequently for osteoporosis therapy. Typically not recommended because of the weak effect on BMD.
c. Efficacy: Nasal calcitonin reduces the incidence of new vertebral fractures by 36%.
d. Adverse effects
i. Nasal (10%–12%): Rhinitis, epistaxis, irritation, nasal sores, dryness, tenderness
ii. Other (3%–5%): Backache, arthralgia, headache
e. Drug interactions: None
f. Dosage: 200 international units/day in one nostril, alternating nostrils daily
g. FDA labeling changes regarding safety in 2014: Malignancies reported to be higher in those treated with calcitonin than in those treated with placebo. Benefits for patient should be discussed with patient and carefully considered.

9. Menopausal estrogen therapy or menopausal estrogen and progestogen therapy; (see Hormone Therapy and Menopause section earlier)
10. Lifestyle modifications
    a. Weight-bearing exercise (e.g., walking, tai chi, dancing, tennis); recommend 30–40 minutes per session most days of the week.
    b. Smoking cessation: Smokers tend to have lower BMD scores than nonsmokers and may reach menopause earlier.
    c. Limiting alcohol intake: Affects fall risk; 2 or more units of alcohol per day associated with 20% of falls at home; no more than 2 units/day or 7 units/week is recommended.
    d. Fall prevention

Table 10. Postmenopausal Osteoporosis Treatment

High Risk/No Prior Fractures			
First Line	**Alternative First Line**	**Increasing or Stable BMD and No Fractures**	**Progression of Bone Loss or Recurrent Fractures**
Alendronate, risedronate, zoledronate	Ibandronate, raloxifene, denosumab[a]	Drug holiday (after 5 yr of PO or 3 yr of IV therapy) Resume therapy with a fracture, BMD declines, BTM rises to pretreatment value	Assess adherence Change to injectable antiresorptive (if on PO therapy) If on injectable or at very high risk, change to abaloparatide, romosozumab, or teriparatide
Very High Risk/Prior Fractures			
First Line			**Alternative First Line**
Denosumab – continue until no longer high risk (up to 10 years); transition to another antiresorptive agent Romosozumab[b] × 1 yr – sequential therapy with PO or injectable antiresorptive agent Abaloparatide or teriparatide[b] × 2 yr – sequential therapy with PO or injectable antiresorptive agent Zoledronate × 6 yr (if stable) – if progressive bone loss or recurrent fractures, change to abaloparatide, teriparatide, or romosozumab			Alendronate, risedronate

[a]Recommended alternative treatment from the ACP 2023 Focused Update.

[b]Recommended first-line treatment from the ACP 2023 Focused Update.

BMD = bone mineral density; BTM = bone turnover marker; IV = intravenous; PO = oral.

Patient Case

2. A 78-year-old man with osteoporosis and no history of fractures has completed 5 years of treatment with alendronate 70 mg orally weekly (bone mineral density [BMD] at diagnosis: −2.0; BMD at 5 years: −1.8). After 1 year of a drug holiday, his BMD is −2.1. Which treatment is best to recommend?
   A. Drug holiday continuation.
   B. Zoledronic acid 5 mg intravenously yearly.
   C. Denosumab 60 mg subcutaneously every 3 months.
   D. Teriparatide 20 mcg subcutaneously daily.

III. DRUGS IN PREGNANCY

A. Definitions and Overview
   1. Teratogen: Drug or environmental agent with the potential to cause abnormal fetal growth and development
   2. Teratogenicity: Capability of producing congenital abnormalities, major or minor malformations

B. Causes of Defects
   1. Genetic predisposition 25%
   2. Drug 2%–3%
   3. Unknown 72%–73%

C. Factors That Influence Risk of Medication Use in Pregnancy
   1. Embryonic stage at exposure
   2. Medication dose and duration
   3. Simultaneous exposure to other drugs that may increase or decrease medication concentrations
   4. Timing of exposure
      a. 1 month before conception: Folic acid 0.4 mg or more taken daily to prevent neural tube defects
      b. Around time of conception and implantation
      c. First 12–15 days after conception: If one cell is damaged, another can assume its function.
      d. First 3 months: Physical malformations
      e. Throughout pregnancy: Functional and behavioral defects because brain development occurs throughout pregnancy.
   5. Factors for placental transport
      a. Molecular weight of drug less than 400–600 Da crosses placenta; most drugs weigh 250–400 Da.
      b. Degree of protein binding; lower in fetus, so more free-drug concentration.
      c. Maternal and fetal blood flow usually equivalent; simple diffusion allows fetal drug concentration to be 50%–100% of maternal.
      d. Metabolic activity of the placenta; excretion of medications by the fetus occurs in liver and placenta.

D. Risk Factor Categories
   1. In 1979, the FDA introduced risk categories for drugs used during pregnancy.
   2. The previous FDA pregnancy risk categories appear in Box 1.

Box 1. Previous FDA Pregnancy Risk Categories

A: Controlled studies of women fail to show risk.
B: Animal studies indicate no risk, or animal studies show a risk that has not been shown in human studies.
C: No available studies of women or animals, or animal studies have shown a risk.
D: Positive evidence of fetal risk.
X: Definite fetal risk in animals or women.

   3. The FDA decided current pregnancy risk categories were inadequate; therefore, in 2008 the FDA recommended a new labeling system that became effective June 30, 2015 that includes the following:
      a. Pregnancy (includes labor and delivery)
         i. Fetal risk summary
         ii. Clinical considerations
         iii. Data section
         iv. Information for exposure registries
      b. Lactation
      c. Females and males of reproductive potential

E. Factors to Consider When Initiating Medications in Pregnant Women (Boxes 2, 3, 4, and 5)
   1. Risk-benefit ratio
   2. Is drug necessary?
   3. Most effective agent with least risk
   4. Lowest effective dosage for shortest possible duration
   5. Health of mother without drug

Box 2. Selected Known Teratogens

Alcohol	Mercury
Androgens	Methimazole
Angiotensin-converting enzyme inhibitors	Methotrexate
Angiotensin II receptor blockers	Paroxetine
Anticonvulsants	Penicillamine
Antineoplastics	Statins
Cocaine	Tetracyclines
Diethylstilbestrol	Thalidomide
Fluconazole (high doses)	Vitamin A (higher than recommended daily doses)
Iodides	Warfarin
Isotretinoin	
Lead	
Lithium	

Box 3. Examples of Drugs Used in Pregnancy: If Benefit Outweighs Risk

Acetaminophen
Cephalosporins
Cetirizine
Erythromycin
Penicillin
Pyridoxine/doxylamine

Box 4. Some Drugs with Known Pregnancy Risks: Should Be Used with Caution

Aminoglycosides	Diuretics
Antithyroid drugs	Isoniazid
Aspirin[a]	Narcotic analgesics (chronic)
Barbiturates	Nicotine
Benzodiazepines	NSAIDs
Caffeine	Oral hypoglycemics
Chloramphenicol	β-Blockers

NSAIDs = nonsteroidal anti-inflammatory drugs

[a]Daily low-dose aspirin (81 mg/day) is recommended in women at high risk of pre-eclampsia. This dose is considered safe and associated with a low likelihood of serious maternal and/or fetal complications.

Box 5. Types of Adverse Effects After Fetal Drug Exposure

Cancer	Renal dysfunction
Developmental delay or deficiency	Seizures
Fetal death	Sexual or reproductive dysfunction
Growth retardation	Teratogenic abnormalities
Hematologic abnormalities	Thyroid dysfunction
Low birth weight for gestational age	Withdrawal
Metabolic abnormalities	

F. Resources for Medication Use During Pregnancy
   1. Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk, 12th Edition.Wolters Kluwer, 2021.
      a. Available as a textbook or online by subscription to Facts & Comparisons eAnswers online and Lexi-Comp.
      b. Provides information about medication use during pregnancy and lactation.
   2. TERIS (Teratogen Information System, http://depts.washington.edu/terisdb/) and Shepard's Database
      a. Available on its own by subscription or by a subscription to Micromedex Solutions.
      b. Provides access to the Clinical Teratology Web (http://depts.washington.edu/terisdb/terisweb/index.html) and has a list of several textbook references and websites not all listed here.
   3. Diseases, Complications, and Drug Therapy in Obstetrics: A Guide for Clinicians. American Society of Health-System Pharmacists, 2009.
      a. Available as a textbook.
      b. Provides information on chronic disease management in pregnancy.
   4. Organization of Teratology Information Specialists (OTIS): MotherToBaby (http://mothertobaby.org/)
      a. Available online by subscription.
      b. Has some resources available to public and providers such as information sheets.
      c. Free hotline for questions (866-626-6847) or e-mail an expert.
   5. Micromedex Solutions: REPROTEXT and REPROTOX
      a. Available by purchase.
      b. Provides information about pregnancy, teratogenicity, and lactation and medication use.

IV. DRUGS IN LACTATION

A. Drugs That Decrease Milk Supply (Box 6)

Box 6. Selected Drugs That Decrease Milk Supply

Androgens	Monoamine oxidase inhibitors (MAOIs)
Bromocriptine	Nicotine
Ergot alkaloids	Pyridoxine
Estrogen	Sympathomimetics
Levodopa	

B. Drugs That Increase Milk Production (Galactagogues) (Box 7)

Box 7. Selected Drugs That Increase Milk Production (Galactagogues) (may or may not be safe in breastfeeding)

Amoxapine	Methyldopa
Antipsychotics	Metoclopramide
Cimetidine	Reserpine

C. Ways to Minimize Effects of Drugs During Breastfeeding
   1. Choose drugs with short half-lives.
   2. Administer drug immediately after a feeding or before a long sleep period.
   3. Consider whether the drug is given to neonates.
   4. Consider age and health status of the infant (e.g., concomitant medical conditions, preterm birth).
   5. Short-term drug: Mother can pump and discard milk ("pump and dump").

D. Safe and Unsafe Drugs in Breastfeeding (Boxes 8 and 9)

Box 8. Some Drugs Contraindicated in Breastfeeding According to the American Academy of Pediatrics

Amphetamines	Pain medications (common ones include oxycodone, pentazocine, and meperidine)
Antineoplastics	
Benzodiazepines	
Bromocriptine	
Cocaine	Yohimbe
Drugs of abuse	Herbs that lack safety data (chamomile, black cohosh, blue cohosh, chaste tree, echinacea, ginseng, ginkgo, St. John's wort, valerian)
Ergotamine	
Kava	
Lithium	
Nicotine	

Box 9. Relatively Safe Agents During Lactation

Analgesics (ibuprofen, acetaminophen)
Antibiotics (penicillins, cephalosporins, erythromycins)
Caffeine (in moderation [1 or 2 cups/day])
Insulin

E. Specific Resources for Drug Information Regarding Lactation
   1. LactMed (Drugs and Lactation Database; www.ncbi.nlm.nih.gov/books/NBK501922/)
      a. Available through the U.S. National Library of Medicine.
      b. Available without purchase or subscription, although information is being incorporated in other databases.
      c. Provides information about safety of medication use during lactation and provides alternative recommendations.
   2. Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk, 12th Edition. Wolters Kluwer, 2021.
      a. Available as a textbook or by subscription to Facts & Comparisons eAnswers online.
      b. Provides information about medication use during pregnancy and lactation.

3. Hale T. Medications and Mothers' Milk
    a. Available by purchase; online site: www.halesmeds.com
    b. Provides information on medication use in lactation with a scoring system of safety.
        i. L1: Safest. Drug has been taken by many breastfeeding mothers with no observed increase in adverse effects in the infant
        ii. L2: Safer. Drug has been studied in a limited number of breastfeeding women with no increase in adverse effects in the infant
        iii. L3: Moderately safe. No controlled studies in breastfeeding women; however, adverse effects in the infant are possible
        iv. L4: Possibly hazardous. Positive evidence of risk to a breastfed infant or to breast milk production
        v. L5: Contraindicated. Studies of breastfeeding mothers have shown that there is risk to the infant, or there is a high risk of causing significant harm to the infant.
4. Micromedex solutions: REPROTEXT and REPROTOX
    a. Available by purchase.
    b. Provides information about pregnancy, teratogenicity, and lactation and medication use.
5. Organization of Teratology Information Specialists OTIS: MotherToBaby (http://mothertobaby.org/)
    a. Available online by subscription.
    b. Has some resources available to public and providers such as information sheets.
    c. Free hotline for questions (866-626-6847) or e-mail an expert.

Patient Case

3. A patient is currently breast/chestfeeding their infant and is prescribed benzonatate for a cough. This medication is identified as having a Hale's lactation risk category of L4. Which explanation is most appropriate?
    A. Safest option according to large amounts of clinical data; limited risk to infants.
    B. Generally safe according to limited amounts of clinical data; limited risk to infants.
    C. Possibly hazardous according to clinical data showing risk to the infant; benefits may be acceptable despite the risk.
    D. Contraindicated because of clinical data showing significant risk to the infant; risk clearly outweighs any benefit.

V. COMMON CONDITIONS DURING PREGNANCY

A. Morning Sickness
    1. Nausea and vomiting associated with pregnancy
    2. Usually during first trimester, but can last throughout pregnancy.
    3. Usually occurs upon rising and diminishes as day progresses
    4. Cause: Unknown, although various theories have been proposed
    5. Hyperemesis gravidarum: Severe nausea and vomiting leading to dehydration and malnutrition.
    6. Nonmedical treatment: First line
        a. Eat saltine crackers.
        b. Keep stomach from becoming completely empty.
        c. Eat small, dry meals.
        d. Avoid spicy and odorous foods.

7. Symptomatic treatment
    a. Doxylamine and pyridoxine (Diclegis: doxylamine succinate 10 mg and pyridoxine hydrochloride 10 mg; dosage 2 tablets orally at bedtime daily. Maximum dosage: One tablet in the morning, one mid-afternoon, and two at bedtime. Bonjesta: doxylamine succinate extended release 20 mg and pyridoxine hydrochloride 20 mg; maximum dosage: 1 tablet in the morning, 1 tablet at bedtime) – considered first-line treatment after nonpharmacologic treatment.
        i. Diclegis and Bonjesta are the only FDA-approved medications for nausea and vomiting in pregnancy. Diclegis is a delayed-release formulation and Bonjesta is an extended-release formulation. Because of the cost or insurance coverage, physicians and patients have attempted off-label use of over-the-counter 12.5 mg doxylamine plus 10–25 mg pyridoxine; however, the efficacy of treatment appears diminished.
    b. Pyridoxine: Considered first-line treatment after nonpharmacologic treatment (with or without doxylamine).
    c. Dimenhydrinate
    d. Diphenhydramine
    e. Ondansetron: Only if nausea and vomiting not controlled with first-line agents; possibility of a slight increase in cardiac birth defects, mainly septal defects; best to avoid if possible, especially during first 10 weeks of gestation (Obstet Gynecol 2018;131:e15-e30).
    f. Metoclopramide – Only if nausea and vomiting not controlled with first-line agents.
    g. Phenothiazines – Only if nausea and vomiting not controlled with first-line agents.

B. Heartburn
    1. Occurs in latter half of pregnancy.
    2. Cause: Enlarged uterus puts pressure on stomach, and esophageal sphincter relaxes.
    3. Nonmedical treatment
        a. Smaller, more frequent meals
        b. Avoid food and liquids 3 hours before bed.
        c. Elevate head of bed with blocks.
    4. Symptomatic relief
        a. Antacids
            i. Magnesium hydroxide
            ii. Aluminum hydroxide (overuse may lead to neurotoxicity)
            iii. Calcium carbonate
        b. Sucralfate: Not absorbed in GI tract.
        c. Second line: Famotidine, proton pump inhibitors

C. Constipation
    1. Cause: Decreased peristalsis
    2. Nonmedical treatment
        a. Increase high-fiber foods.
        b. Increase fluid intake to eight 8-oz glasses of water a day.
        c. Increase exercise.
    3. Symptomatic relief
        a. Stool softeners (check that prenatal vitamin does not already contain docusate)
        b. Bulk laxatives: Not absorbed.
        c. Stimulants: Not recommended as first-line therapy.
        d. Avoid mineral oil: Impairs vitamin K absorption and could cause hypoprothrombinemia.

D. Hemorrhoids
   1. Caused by constipation and increased venous pressure below uterus
   2. Correct constipation with stool softeners, appropriate hydration, and dietary fiber.
   3. Sitz baths
   4. Avoid topical anesthetics and steroids, not well studied. May be used short-term under a physician's direction (Can Fam Physician 2008;54:189-90).

E. Headache
   1. Cause: Hormone fluctuations
   2. Therapy
      a. Rest, ice packs
      b. Acetaminophen
   3. Drugs to avoid
      a. Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs)
      b. Triptans, ergotamine

F. Coagulation Disorders
   1. Anticoagulation necessary
      a. History of VTE
      b. Prosthetic heart valve
      c. Deficiencies of clotting factors
      d. Antiphospholipid antibodies
   2. Therapy
      a. Avoid warfarin (known teratogenicity) and direct oral anticoagulants (lack of data).
      b. Heparin or low-molecular-weight heparin (monitor for osteoporosis if heparin is used long term)
      c. Low-molecular-weight heparin preferred to heparin (Obstet Gynecol 2018;132:e18-34; Chest 2012; 141:e691S-736S).
      d. Dosing
         i. Prophylactic
            (a) Enoxaparin 40 mg subcutaneously daily
            (b) Dalteparin 5000 units subcutaneously daily
            (c) Tinzaparin 4500 units subcutaneously daily
            (d) Heparin 5000–7500 units subcutaneously every 12 hours for first trimester, 7500–10,000 units subcutaneously every 12 hours for second trimester, and 10,000 units subcutaneously every 12 hours for third trimester unless activated partial thromboplastin time (aPTT) is elevated
         ii. Therapeutic
            (a) Enoxaparin 1 mg/kg subcutaneously every 12 hours
            (b) Dalteparin 200 units/kg subcutaneously daily or 100 units/kg subcutaneously every 12 hours
            (c) Tinzaparin 175 units/kg subcutaneously daily
            (d) Heparin 10,000 units subcutaneously every 12 hours with target activated partial thromboplastin time (aPTT) range (1.5–2.5) 6 hours after injection or adjusted-dose unfractionated heparin subcutaneously every 12 hours, with mid-interval aPTT target of 2 times the control
      e. May consider switching LMWH to heparin at 36 weeks of gestation to permit induction of anesthesia during labor and delivery because of the lower risk of an epidural or spinal hematoma with regional anesthesia and a greater ease of heparin reversal by protamine sulfate.

f. Prophylaxis with LMWH or UFH should be discontinued 12 hours before cesarean section or vaginal delivery. Therapeutic doses should be discontinued 24 hours before cesarean section or vaginal delivery.
g. Consider timing of catheter placement for anesthesia as well.
h. Continue anticoagulation for 6 weeks postpartum.
i. For women experiencing heparin-induced thrombocytopenia, consider fondaparinux; limited data and crosses placenta.

G. Gestational Diabetes (GD)
1. Diagnostic approaches (Table 11)

Table 11. GD Diagnostic Approaches

Approach	Criteria	Organizations	Comments
Two-step approach	50-g oral glucose test Plasma measured 1 hr after If ≥ 130 mg/dL or 140 mg/dL, give 100-g, 3-hr glucose test	ACOG, NIH	Given at 24–28 weeks' gestation; may be earlier in those with risk factors[a]
One-step approach	Obtain A1C at initial prenatal visit; if elevated, patient has overt diabetes; no further testing 75-g oral glucose test Plasma measured at fasting, 1 and 2 hr	IADPSG, ADA	Given at 24–28 weeks' gestation; should be fasting for at least 8 hours

[a]Select risk factors include: family history of diabetes, personal history of GD, hypertension, conditions associated with insulin resistance
ADA = American Diabetes Association; GD = gestational diabetes; IADPSG = International Association of the Diabetes and Pregnancy Study Groups; NIH = National Institutes of Health.

2. Diagnostic criteria
a. Two-step approach: 100-g 3-hour oral glucose test (OGTT) used after initial screening; if greater than or equal to values at two or more points, consider GD (Table 12).

Table 12. 3-Hr Oral Glucose Test Reference Range

Time	Plasma Glucose Concentration (mg/dL) Carpenter-Coustan	Plasma Glucose Concentration (mg/dL) National Diabetes Data Group
Fasting	95	105
1 hr	180	190
2 hr	155	165
3 hr	140	145

b. One-step approach: Based on 75-g 2-hour oral glucose test (Table 13)

Table 13. Glucose Reference Range for 2-Hr Oral Glucose Test

Time	Plasma Glucose
Fasting	92 mg/dL
1 hr	≥ 180 mg/dL
2 hr	≥ 153 mg/dL

3. Treatment approaches
    a. Diet and lifestyle modifications. May be referred to as A1GD when able to be controlled without medications.
    b. Pharmacologic management is necessary for some people with GD. They would be considered to have type A2GD.
        i. Insulin (first line): None of the currently available human insulin preparations have been shown to cross the placenta. Starting dose is typically 0.7–1.0 units/kg/day. No specific insulin regimen has been recommended over another for treatment of GD in pregnancy. Insulin is considered the preferred treatment when pharmacologic treatment of GD is indicated. In women who decline insulin or who the obstetrician believes are unable to safely administer insulin, metformin is a reasonable alternative. Previous meta-analyses have noted increased risks of macrosomia and hypoglycemia with glyburide compared with insulin. Observational studies have reported higher rates of preeclampsia, hyperbilirubinemia, and stillbirth with the use of glyburide as compared with insulin (BMJ 2015;350:h102; Am J Obstet Gynecol 2005;193:118-24).
        ii. Sulfonylureas (glyburide) may be used in patients unable to use insulin injections; however, evidence shows they may be inferior to insulin and metformin because of increased risk of hypoglycemia and macrosomia in the infant. In addition, they have been shown to cross the placenta (Diabetes Care 2021;44:S200-10). ACOG recommends against use as first-line therapy stating that glyburide does not yield similar outcomes as insulin (Obstet Gynecol 2018;131:e49-64).
        iii. Metformin may have advantage over glyburide; studies are ongoing, (not first line), associated with some risk of premature birth and also may cross the placenta; may emerge as possible treatment, according to ACOG (Diabetes Care 2021;44:S200-10; Obstet Gynecol 2018;131:e49-64).

H. Pregnancy-Induced Hypertension: Hypertension occurring after 20 weeks' gestation
    1. Gestational hypertension: 140/90 mm Hg or more, occurring at least 4 hours apart on two different occasions in women with previously normal blood pressure without proteinuria or pathologic edema
    2. Preeclampsia: Hypertension plus proteinuria (300 mg/dL or more every 24 hours, or protein/creatinine ratio of 3.0 mg/dL or more, or dipstick reading of 2+), any other severe features of preeclampsia such as systolic blood pressure higher than 160 mm Hg or diastolic blood pressure higher than 110 mm Hg at least 4 hours apart and on two occasions (unless antihypertensive treatment was started before this time), thrombocytopenia (platelet count less than 100,000/mm^3), impaired liver function (increased levels of liver function enzymes to twice normal or severe right upper quadrant pain or epigastric pain refractory to medication and not accounted for by other diagnoses), new development of renal insufficiency (serum creatinine greater than 1.1 mg/dL or a doubling of the serum creatinine without evidence of other renal disease), pulmonary edema, new development of headache that does not respond to therapy and has no known cause, or visual changes (ACOG Chronic Hypertension in Pregnancy. Obstet Gynecol 2019;133:e26-e50; ACOG Gestational Hypertension and Preeclampsia. Obstet Gynecol 2019;133:e1-e25).
    3. Eclampsia: Includes the features of preeclampsia with the addition of tonic-clonic seizures
    4. Chronic hypertension: Preexisting hypertension before 20 weeks' gestation
    5. Chronic hypertension with superimposed preeclampsia: New-onset proteinuria after 20 weeks, sudden 2- to 3-fold increase in proteinuria, sudden increase in blood pressure, increased aspartate transaminase–alanine transaminase, thrombocytopenia
    6. Prevention: Women at high risk of preeclampsia development may take aspirin 81–162 mg beginning in late first trimester; a study showed lower incidence of preeclampsia development in women who were administered 150 mg of aspirin from 11 to 14 weeks of gestation to 36 weeks. For women at high risk of preeclampisa, low-dose aspirin should be initiated between 12–28 weeks gestation (optimally before 16 weeks) and continued daily until delivery.

7. Risk of preeclampsia and aspirin use
    a. Recommend low-dose aspirin if the patient has one or more of these high-risk factors (history of preeclampsia, multifetal gestation, chronic hypertension, type 1 or 2 diabetes, renal disease, or autoimmune disease)
    b. Consider low-dose aspirin if the patient has more than one of these moderate-risk factors: nulliparity, BMI greater than 30 kg/m^2, family history of preeclampsia in mother or sister, older than 35 years, personal history of adverse pregnancy outcomes, more than a 10-year pregnancy interval.
    c. Do not recommend low-dose aspirin in previous uncomplicated full-term delivery (Obstet Gynecol 2019;133:e1-e25; N Engl J Med 2017;377:613-22).
8. Treatment
    a. Delivery if at term
    b. If not at term, get bed rest and monitor blood pressure.
    c. Severe preeclamptic, parenteral magnesium sulfate to prevent seizures
    d. Labetalol (oral), nifedipine (oral, extended release) are first-line therapies.
    e. Emergent therapy for acute-onset, severe hypertension during pregnancy and the postpartum period: Labetalol (intravenous), hydralazine (intravenous), nifedipine (oral, immediate release; concern for serious adverse effects when used simultaneously with magnesium)
    f. Medications to avoid: Angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, renin inhibitors, and mineralocorticoid receptor antagonists

I. Preterm Labor
1. Definitions
    a. Term labor: Weeks 37–40
    b. Preterm labor: Uterine contractions with cervical changes before week 37
2. Nonpharmacologic treatment
    a. Inhibition of labor not usually tried before week 20.
    b. Bed rest, hydration, and sedation
3. Prophylaxis at 16–36 weeks for patients with a history of preterm labor: 17-hydroxyprogesterone caproate 250 mg intramuscularly every week
4. Tocolytic drugs (inhibit uterine contractions), especially if cervix dilated less than 4 cm and membranes intact; short term use only
    a. β-Agonists
        i. Terbutaline: Often subcutaneously
        ii. Adverse effects: Hypotension, tachycardia, hypokalemia, tremor, nervousness, angina, headache, hypoglycemia in patients with diabetes
        iii. FDA warning for use beyond 48 hours because of severe adverse effects in the mother such as elevated heart rate, transient hyperglycemia, hypokalemia, cardiac arrhythmias, pulmonary edema, and myocardial ischemia. Warning also against use of oral terbutaline for preterm labor because of lack of efficacy.
    b. Magnesium sulfate
        i. Inhibits uterine activity by antagonism of calcium.
        ii. Anticonvulsant in eclampsia.
        iii. Serum magnesium concentrations 5–8 mEq/L. Monitor closely for signs of toxicity because the therapeutic range is close to the range that may cause respiratory or cardiac depression. Toxicity may be reversed with calcium gluconate (intravenously).
        iv. May be drug of choice in patients with diabetes.

c. Prostaglandin synthetase inhibitors (NSAIDs)
    i. Prostaglandins are in amniotic fluid during labor and delivery but not during pregnancy.
    ii. Indomethacin: Oral or rectal
    iii. Adverse effects: Premature closure of ductus arteriosus, necrotizing enterocolitis, intracranial hemorrhage, renal dysfunction
    iv. Limit use to 72 hours.
d. Calcium channel blockers
    i. Calcium necessary for muscle contraction; limit use to 48 hours, should be used with caution in combination with magnesium sulfate due to a risk of reduced heart rate, contractility, and left ventricular systolic pressure.
    ii. Nifedipine: Typically used; use caution when administered near administration of magnesium, may result in hypotension.
    iii. Verapamil: Large doses needed that mother usually cannot tolerate.

J. Induction of Labor
1. Induction indicated when:
    a. Severe maternal infection
    b. Uterine bleeding
    c. Preeclampsia or eclampsia
    d. Diabetes
    e. Macrosomia
    f. Maternal renal insufficiency
    g. Premature rupture of membranes after week 36
    h. Evidence of placental insufficiency
    i. Postdatism (more than 42 weeks)
2. Inducing agents
    a. Oxytocin
        i. Drug of choice for labor induction
        ii. Intravenous administration
        iii. Adverse effects: Uterine rupture, uteroplacental hypoperfusion, fetal distress from hypoxia
    b. Ergot alkaloids
        i. Not used to induce labor at term or late in pregnancy.
        ii. Violent, sustained uterine contractions
        iii. Decrease postpartum or postabortion bleeding
        iv. Oral and parenteral
    c. Prostaglandins: Used primarily for cervical ripening
        i. Dinoprostone also known as PGE2 (prostaglandin E_2)
            (a) Vaginal gel or insert, sometimes compounded suppositories
            (b) Applied to cervix
            (c) Adverse effects: Headache, nausea, vomiting, diarrhea, abdominal pain, and uterine hyperstimulation
        ii. Misoprostol (off-label use), also known as PGE1 (prostaglandin E_1)
            (a) Available orally and vaginally
            (b) Adverse effects: Headache, nausea, vomiting, diarrhea, abdominal pain, and uterine hyperstimulation

K. Medication Abortion
   1. Can be used to terminate a pregnancy up to 70 days (10 weeks) gestation; calculated from the first day of the last menstrual period
   2. Contraindications
      a. Presence of IUD
      b. Long-term corticosteroid use
      c. Use of anticoagulant therapy
      d. Blood coagulation disorder
      e. Ectopic pregnancy
   3. Medication regimen
      a. Combination of mifepristone and misoprostol
      b. Mifepristone
         i. Progesterone antagonist that competitively inhibits progesterone at receptor sites
         ii. Dose: 200 mg tablet orally for 1 dose
      c. Misoprostol
         i. Prostaglandin analogue that causes cervical softening, dilation, and uterine contractions
         ii. Dose: 800 mcg (4 tablets) bucally (place 2 tablets inside each cheek for 30 minutes, then swish with water and swallow)
         iii. Taken 24–48 hours after mifepristone
         iv. Regimens without FDA approval include use of misoprostol alone

Patient Cases

4. A 28-year-old woman is 8 weeks into her first pregnancy. She has had nausea and vomiting for 1 week that have not improved with chilled beverages, dietary changes, or trigger avoidance. She has not tried any pharmacologic options. Which initial recommendation is most appropriate?
   A. Doxylamine.
   B. Metoclopramide.
   C. Ondansetron.
   D. Pyridoxine.

5. A 31-year-old woman who is 26 weeks pregnant has a plasma glucose concentration of 175 mg/dL after her 75-g 2-hour oral glucose tolerance test (OGTT). She completes a 100-g, 3-hour OGTT with a fasting plasma glucose of 115 mg/dL, a 2-hour plasma glucose of 189 mg/dL, and a 3-hour glucose of 152 mg/dL. She has no history of gestational diabetes. Which treatment recommendation is most appropriate?
   A. Lifestyle modifications with carbohydrate counting.
   B. Glyburide.
   C. Metformin.
   D. Basal-bolus insulin.

VI. OVERVIEW OF CONTRACEPTION

A. Epidemiology
   1. About 45% of pregnancies are unintended in the United States, with about 42% of those resulting in abortions (according to 2011 data, N Engl J Med 2016;374:843-52).
   2. Among female contraceptive users in 2018, 28% were using female permanent contraception, 21% were using pills and 13% were using an intrauterine device (IUD) (www.guttmacher.org/fact-sheet/contraceptive-method-use-united-states).

B. Physiology Review: Menstrual Cycle
   1. Follicular phase: GnRH stimulates the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH); FSH stimulates estradiol secretion and stimulates follicles to develop; one in particular will become the dominant follicle (in the first half of cycle); later in follicular phase, LH causes an increase in androgen values.
   2. Ovulation: Typically occurs midcycle; mature follicle ruptures; a surge in LH occurs just before ovulation.
   3. Luteal phase: Progesterone is the more dominant hormone in the second half of cycle.
   4. Menses: Hormones have decreased, and withdrawal bleeding occurs if a woman does not become pregnant.

C. Factors in Selecting Contraception
   1. Effectiveness
      a. Theoretical: Method failure if patient uses method perfectly (e.g., COCs have 99% theoretical effectiveness in preventing pregnancy)
      b. Actual: Combines method failure plus patient failure (e.g., COCs have 93% actual effectiveness when average patient use is considered). Sometimes referred to as "typical use" rates.
   2. Importance of not being pregnant
   3. Likelihood and ability to adhere
   4. Frequency of intercourse: Frequent versus infrequent
   5. Age may affect adherence or adverse effect risks.
   6. Cost and ability to pay
   7. Adverse effects
   8. Perceptions, misperceptions, risk-benefit
   9. Concomitant drug use
   10. Health status and habits
   11. Patient preference
   12. Cultural preferences
   13. Religious influences

D. Methods of Birth Control
   1. Abstinence
   2. Male or female sterilization
   3. Natural family planning
   4. Spermicides
   5. Barrier methods
      a. Diaphragm or cervical cap
      b. Condom
      c. Female condom
      d. Sponge
   6. Hormonal contraception
      a. Combined contraceptives—contain both an estrogen and a progestin
         i. Combined oral contraceptive (COC) pills
         ii. Transdermal patch
         iii. Vaginal ring
      b. Progestin-only—does not contain any estrogen
         i. Progestin-only pill (POP or minipill)
         ii. Progestin-only injectable
         iii. Implanted rod

7. Intrauterine device (IUD)
    a. Copper
    b. Progestin-containing
8. Lactic acid, citric acid, and potassium bitartrate vaginal gel (PHEXXI)
9. Emergency contraception

Patient Case

6. A woman takes ethinyl estradiol 35 mcg/norgestimate 0.25 mg (Sprintec-28) 1 tablet orally daily as her contraceptive. She usually takes her pill at 9:00 a.m., but at 5:00 p.m. today, she realizes she did not take her dose for the day. Which is the best counseling information for her?

    A. Take the late dose now; use a backup method for the next 7 days.

    B. Take the late dose now; no backup method is needed.

    C. Skip the late dose and take the next dose at the regular time; use a backup method for the next 7 days.

    D. Skip the late dose and take the next dose at the regular time; no backup method is needed.

VII. COMBINED HORMONAL CONTRACEPTIVES

A. Indications
    1. FDA label approved
        a. Prevent pregnancy
        b. Acne (Estrostep Fe, Ortho Tri-Cyclen, YAZ, Beyaz)
        c. Premenstrual dysphoric disorder (YAZ, Beyaz)
    2. Off-label use
        a. Hirsutism
        b. Cycle control
        c. Headaches
        d. Premenstrual syndrome
        e. Iron-deficiency anemia
        f. Relief of menstrual cramps

B. Components
    1. Estrogen
        a. Type of estrogens available in products in the United States
            i. Ethinyl estradiol (in almost all products), estradiol valerate, estetrol
            ii. Mestranol (not used often)
        b. Pharmacologic actions of estrogen in contraceptives
            i. Feeds back to the pituitary, inhibiting FSH and ovulation.
            ii. Increases aldosterone concentrations, results in increased sodium and water retention.
            iii. Increases sex hormone–binding globulin, which is produced in the liver and binds free androgens; this may result in clearing up hormone-mediated acne and unwanted facial hair or hirsutism in women.
        c. Adverse effects attributed to estrogen
            i. Nausea, vomiting
            ii. Bloating, edema
            iii. Irritability
            iv. Cyclic weight gain

v. Cyclic headache
vi. Hypertension
vii. Breast fullness, tenderness

2. Progestin
   a. Progestins have three basic characteristics to be considered. Desired progestins tend to have higher progestational selectivity and lower androgenic and antiestrogenic activity.
      i. Progestational: Prevent ovulation; lessen bleeding (examples with higher activity: desogestrel, etonogestrel, levonorgestrel)
      ii. Androgenic: Contributes to acne and hirsutism (examples with higher activity: levonorgestrel, norgestrel)
      iii. Antiestrogenic: Contributes to androgenic side effects (examples with higher activity: norethindrone, ethynodiol diacetate)
   b. Types of progestins available in products in the United States
      i. Desogestrel
      ii. Dienogest
      iii. Drospirenone
      iv. Ethynodiol diacetate
      v. Etonogestrel
      vi. Levonorgestrel
      vii. Norelgestromin
      viii. Norethindrone
      ix. Norethindrone acetate
      x. Norgestimate
      xi. Norgestrel
      xii. Segesterone acetate
   c. Pharmacologic actions of progestins in contraceptives
      i. Feeds back to pituitary and helps inhibit ovulation (not a main action).
      ii. Causes endometrial atrophy (thinning of uterus lining).
      iii. Thickens cervical mucus (inhibits sperm from traveling).
   d. Adverse effects caused by progestin
      i. Headaches
      ii. Increased appetite
      iii. Increased weight gain
      iv. Depression, fatigue
      v. Changes in libido
      vi. Androgenic adverse effects
         (a) Hair loss, hirsutism
         (b) Acne, oily skin

C. Contraindications for Combined Hormonal Contraceptives
   1. The Centers for Disease Control and Prevention (CDC) medical eligibility criteria are separated into four categories:
      a. Category 1: A condition for which there is no restriction on the use of contraceptive method
      b. Category 2: A condition in which the advantages of using the method generally outweigh the theoretical or proven risks
      c. Category 3: A condition in which the theoretical or proven risks usually outweigh the advantages of using the method
      d. Category 4: A condition that represents an unacceptable health risk if the contraceptive method is used

2. Examples of category 4 contraindications for combined hormonal contraceptives
    a. Less than 21 days postpartum for women with no risk factors for DVT (regardless of breastfeeding status),
    b. Smoker (15 cigarettes or more per day) and/or 35 and older, though conservatively, any smoking can be a risk factor
    c. Blood pressure greater than 160/100 mm Hg
    d. Vascular disease
    e. Current DVT or pulmonary embolism or history of DVT or pulmonary embolism
    f. Complicated diabetes showing nephropathy, neuropathy, or retinopathy
    g. Major surgery with prolonged immobilization
    h. Known thrombogenic mutations
    i. Current or history of ischemic heart disease
    j. Stroke (history of cerebrovascular accident)
    k. Migraine headache with aura
    l. Current breast cancer
    m. Systemic lupus erythematosus with positive or unknown antiphospholipid antibodies
    n. Active cancer (metastatic, receiving therapy, or within 6 months after clinical remission).

D. Adverse Effects (see Estrogen and Progestin sections earlier for specific hormone-causing adverse effects)
1. Discontinuation of hormonal contraceptives was due to:
    a. Bleeding irregularities: 32%
    b. Nausea: 19%
    c. Weight gain: 14%
    d. Mood swings: 14%
    e. Breast tenderness: 11%
    f. Headache: 11%
2. Management of adverse effects
    a. Breakthrough bleeding
        i. Consider new product after trying the product for 3 months, assess adherence.
        ii. If late in the cycle, there is probably not enough progestin; select a regimen with higher progestin activity.
        iii. In general, if breakthrough bleeding occurs, it is best to select a regimen with higher estrogen and progestin activities.
    b. Nausea
        i. More likely to be related to estrogen component.
        ii. Suggest the patient take the pill at night before bed or with food.
        iii. If possible, try the product for 3 months; nausea may subside.
    c. Acne
        i. More likely to be related to the androgenic properties of progestin.
        ii. Select a product with lower androgenic activity.
        iii. Alternatively, select a product with higher estrogen activity.
3. Serious adverse effects (ACHES)
    a. **A**: Abdominal pain; could signal liver problems or gallbladder.
    b. **C**: Chest pain, shortness of breath, coughing up blood; could signal myocardial infarction or blood clot in lung.
    c. **H**: Headaches (severe); could signal stroke, blood clot.
    d. **E**: Eye problems (blurred vision, flashing lights, blindness); could signal optic neuritis, stroke, clots.
    e. **S**: Severe leg pain with or without swelling; could signal DVT.

E. Common Drug Interactions (list not all-inclusive)

Table 14. Common Drug Interactions with Hormonal Contraception

Increase Effect of HC	Decrease Effect of HC	Drugs that Are Increased or Decreased by HC
Ascorbic acid	Amprenavir	Acetaminophen
Atazanavir	Aprepitant	Antidepressants, tricyclic
Atorvastatin	Barbiturates	Aspirin
Ginseng	Bexarotene	Benzodiazepines
Indinavir	Bosentan	β-Blockers
Red clover (may increase or decrease effect of combined HCs)	Carbamazepine	Caffeine
Rosuvastatin	Darunavir	Clofibric acid
Tranexamic acid	Efavirenz	Corticosteroids
Voriconazole	Felbamate	Cyclosporine
	Griseofulvin	Fosamprenavir
	Lopinavir	Lamotrigine
	Modafinil	Levothyroxine
	Mycophenolate mofetil	Morphine
	Nelfinavir	Paclitaxel
	Nevirapine	Salicylic acid
	Oxcarbazepine	Selegiline
	Phenobarbital	Tacrine
	Phenytoin/fosphenytoin	Tacrolimus
	Pioglitazone	Theophyllines
	Primidone	Tizanidine
	Red clover (may increase or decrease effect of combined HCs)	Valproic acid
	Rifamycins	
	Ritonavir	
	Rufinamide	
	Saquinavir	
	St. John's wort	
	Tipranavir	

HC = hormonal contraceptives.

1. Simplified list of drug-drug interactions according to the U.S. Medical Eligibility Criteria for Contraceptive Use 2016 (www.cdc.gov/mmwr/volumes/65/rr/pdfs/rr6503.pdf)
   a. Nucleoside reverse transcriptase inhibitors, maraviroc, HIV integrase strand transfer inhibitors (category 1: before treating any patients, recommend to check specific product information)
   b. Nonnucleoside reverse transcriptase inhibitors (category 1 or 2: before treating any patients, recommend to check specific product information)
   c. Ritonavir-boosted protease inhibitors (category 2; exception: ritonavir-boosted lopinavir)
   d. Protease inhibitors without ritonavir (category 1: indinavir; category 2: – nelfinavir and atazanavir; category 3: fosamprenavir)
   e. Antiepileptics (category 3)

f. Rifampin or rifabutin (category 3)
g. St. John's wort (category 2)
h. Broad-spectrum antibiotics, antifungals, antiparasitics (category 1); U.S. Medical Eligibility Criteria for Contraceptive Use 2016 suggest that no alternative form of contraception is necessary with broad-spectrum antibiotics, but other antibiotics may require an alternative form of contraception (see text that follows)
i. Reported antibiotic cases in the literature: Tetracycline, minocycline, erythromycin, penicillins, and cephalosporins; pharmacokinetic studies have not shown decreased hormonal contraceptive concentrations with tetracycline, doxycycline, ampicillin, metronidazole, quinolones, or fluconazole.
    i. Proposed mechanisms of drug interactions
        (a) Interference of absorption: Ethinyl estradiol is conjugated in the liver, excreted in bile, hydrolyzed by intestinal bacteria, and reabsorbed as an active drug; non–liver enzyme-inducing antibiotics temporarily decrease colonic bacteria and inhibit enterohepatic circulation of ethinyl estradiol. Gut flora have recovered 3 weeks after the introduction of antibiotics.
        (b) Liver enzyme induction (rifampin and griseofulvin): The metabolism of progesterone and estrogen is accelerated.
    ii. Use a backup method (BUM) for the length of antibiotic therapy plus 7 days after discontinuing antibiotic.

F. Types of Contraceptives
1. Oral
    a. COC regimens
        i. Monophasic: Same amount of hormone in pill every day except in placebo pills
        ii. Biphasic: Amount of hormone may change halfway through cycle.
        iii. Triphasic: Amount of hormone changes every week.
        iv. Quadriphasic: Four varying amounts of hormones throughout monthly pack
    b. Dosing
        i. High-dose estrogen: Higher than 35 mcg (up to 50 mcg)
        ii. Low-dose estrogen: Less than 35 mcg (generally 20–35 mcg)
        iii. Very low-dose estrogen: Less than or equal to 10 mcg
    c. Effectiveness: When taken every day at the same time, 99.7% (perfect use), typical use (about 93%) (Contraceptive Technology, 21st ed. New York: Ardent Media, 2018)
    d. Adherence: 68% continue after 1 year
    e. Start methods
        i. Same-day start: Start taking an active pill the first day of menses.
        ii. Sunday start: Start taking an active pill the first Sunday after menses begins (use a BUM for at least 7 days, most conservative for 1 month).
        iii. Quick start: Start taking an active pill at the physician's office or first day of prescription, regardless of menstrual cycle day. Use a BUM for at least 7 days. Most conservative; use a BUM for 1 month. Menses will not begin until all the active pills have been taken.
        iv. When changing pills from brand to brand, start the new pack of pills after finishing the placebo pills (if present) from the old pack.
    f. Counseling
        i. Proper use: Take 1 tablet once daily at the same time every day.
        ii. Adverse effects
            (a) See previous text.

(b) Adverse effects usually subside after 3 months; general recommendation is to stay on a brand for at least 3 months if adverse effects are not excessively bothersome. If still present after about 3 months, consider change in product to a different combination of hormones based on adverse effects being experienced.

iii. Missed doses: Missed COC pill means more than 24 hours between doses.

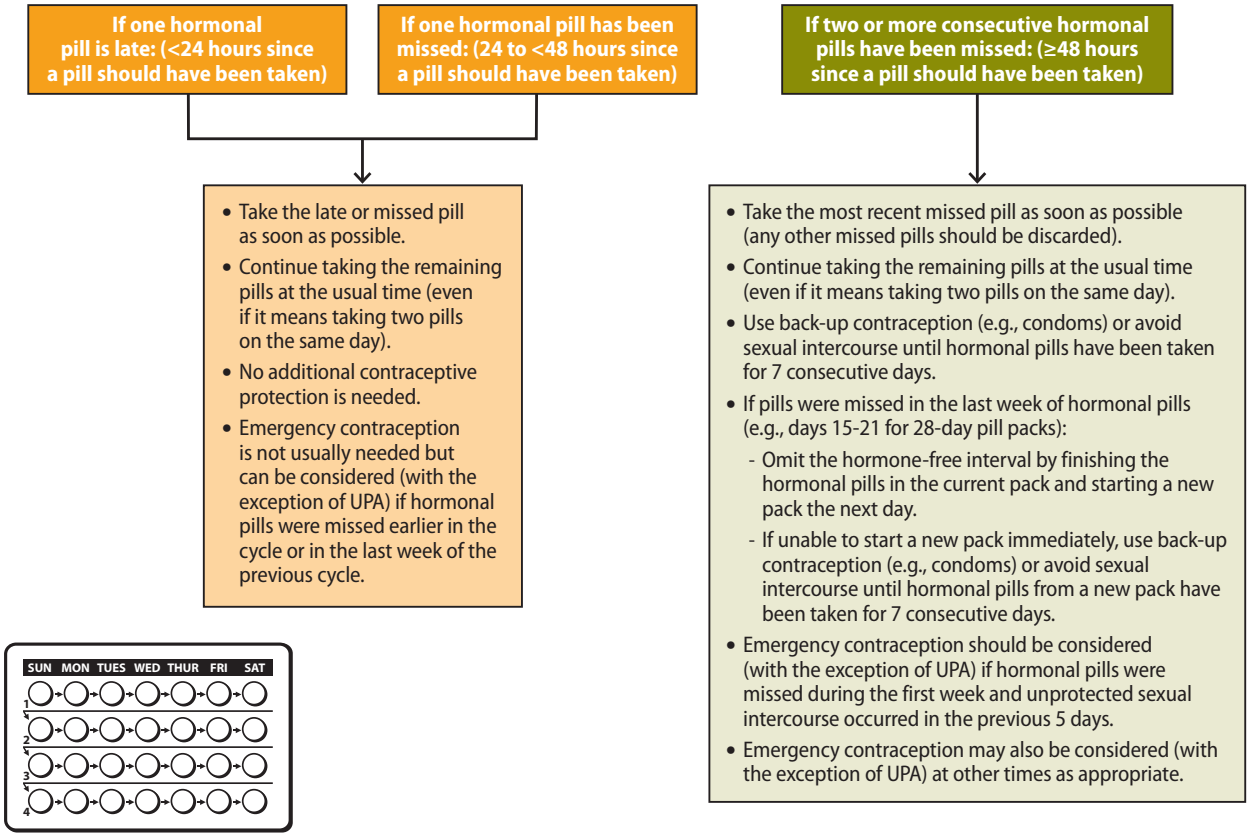

If one hormonal pill is late: (<24 hours since a pill should have been taken)
If one hormonal pill has been missed: (24 to <48 hours since a pill should have been taken)
If two or more consecutive hormonal pills have been missed: (≥48 hours since a pill should have been taken)
• Take the late or missed pill as soon as possible.
• Continue taking the remaining pills at the usual time (even if it means taking two pills on the same day).
• No additional contraceptive protection is needed.
• Emergency contraception is not usually needed but can be considered (with the exception of UPA) if hormonal pills were missed earlier in the cycle or in the last week of the previous cycle.
• Take the most recent missed pill as soon as possible (any other missed pills should be discarded).
• Continue taking the remaining pills at the usual time (even if it means taking two pills on the same day).
• Use back-up contraception (e.g., condoms) or avoid sexual intercourse until hormonal pills have been taken for 7 consecutive days.
• If pills were missed in the last week of hormonal pills (e.g., days 15-21 for 28-day pill packs):
- Omit the hormone-free interval by finishing the hormonal pills in the current pack and starting a new pack the next day.
- If unable to start a new pack immediately, use back-up contraception (e.g., condoms) or avoid sexual intercourse until hormonal pills from a new pack have been taken for 7 consecutive days.
• Emergency contraception should be considered (with the exception of UPA) if hormonal pills were missed during the first week and unprotected sexual intercourse occurred in the previous 5 days.
• Emergency contraception may also be considered (with the exception of UPA) at other times as appropriate.
SUN MON TUES WED THUR FRI SAT
1
2
3
4

Figure 2. Recommended actions after late or missed combined oral contraceptives.

UPA = ulipristal acetate

Source: CDC. Note: Reference to specific commercial products, manufacturers, companies, or trademarks does not constitute its endorsement or recommendation by the U.S. Government, Department of Health and Human Services, or Centers for Disease Control and Prevention. This material is otherwise available on the agency website for no charge.

(b) Package inserts can be consulted for recommendations based on specific products.

g. Drospirenone progestin-containing contraceptives

i. Drospirenone: Analog of spironolactone, similar to spironolactone 25 mg

ii. Exercise caution with drugs that increase potassium such as high doses of NSAIDs, heparin, ACE inhibitors, and potassium-sparing diuretics.

iii. No diuretic effect, has antimineralocorticoid effects, decreases bloating effect of ethinyl estradiol.

iv. Antiandrogenic: Best for acne, hirsutism, or male pattern balding in women

v. Possible increased risk of DVT, FDA safety communication, April 2012

h. Advantages and disadvantages (Table 15)

Table 15. Advantages and Disadvantages of COCs

Advantages	Disadvantages
Effective	No HIV or STI protection
Easy to use	Patient adherence
Reversible	Expensive
Regular menstrual cycle	Adverse effects
Reduction of several cancers	Circulatory complications
Decreased risk of benign breast tumors	Menstrual cycle changes
Improves acne	Sexual and psychological effects
Sexual enjoyment	Hepatocellular adenoma
Emergency contraception	Gallbladder disease
Transition therapy for perimenopause	Drug interactions

COC = combined oral contraceptive (tablet); HIV = human immunodeficiency virus; STI = sexually transmitted infection

2. Transdermal patch (Xulane, Zafemy, Twirla)
   a. Patch placed on skin; Xulane /Zafemy delivers 150 mcg of norelgestromin/35 mcg ethinyl estradiol (provides 60% more estrogen exposure than 35-mcg oral tablet of ethinyl estradiol); Twirla delivers 120 mcg of levonorgestrel/30 mcg of ethinyl estradiol.
   b. Effectiveness
      i. Similar to pills (7% failure rate for typical use, 0.3% for perfect use)
      ii. May be less effective in women weighing more than 198 lb (90 kg); the US MEC does not preclude the use of any product based on weight alone.
   c. Adherence: Better adherence rates than pill, especially in teens
   d. Counseling
      i. Proper use
         (a) Place patch on a dry, hairless area of upper arm, shoulder, abdomen, or buttocks. Should not be placed on the breast. Rotate site of patch each week.
         (b) One patch per week for 3 weeks; week 4 is patch free (menses will occur then)
      ii. Adverse effects
         (a) Higher incidence of blood clots
         (b) Site irritation from the patch
         (c) See adverse effects mentioned earlier in text.
      iii. Missed doses (Figure 3)

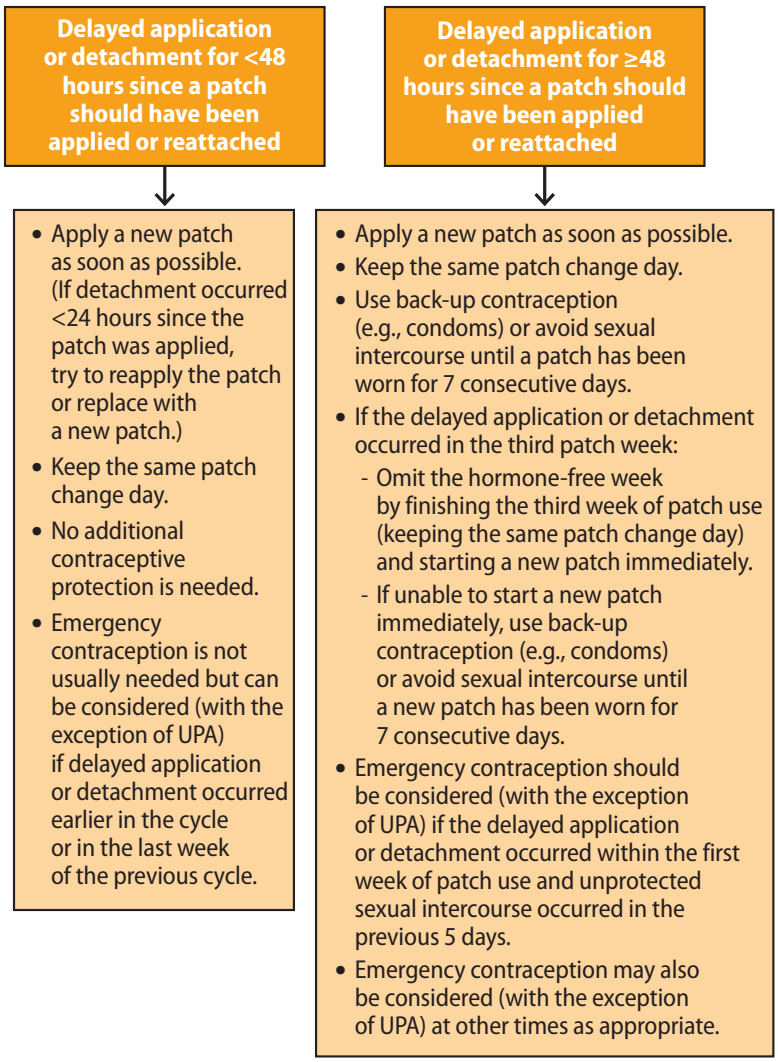

Delayed application or detachment for <48 hours since a patch should have been applied or reattached
Delayed application or detachment for ≥48 hours since a patch should have been applied or reattached
• Apply a new patch as soon as possible. (If detachment occurred <24 hours since the patch was applied, try to reapply the patch or replace with a new patch.)
• Keep the same patch change day.
• No additional contraceptive protection is needed.
• Emergency contraception is not usually needed but can be considered (with the exception of UPA) if delayed application or detachment occurred earlier in the cycle or in the last week of the previous cycle.
• Apply a new patch as soon as possible.
• Keep the same patch change day.
• Use back-up contraception (e.g., condoms) or avoid sexual intercourse until a patch has been worn for 7 consecutive days.
• If the delayed application or detachment occurred in the third patch week:
- Omit the hormone-free week by finishing the third week of patch use (keeping the same patch change day) and starting a new patch immediately.
- If unable to start a new patch immediately, use back-up contraception (e.g., condoms) or avoid sexual intercourse until a new patch has been worn for 7 consecutive days.
• Emergency contraception should be considered (with the exception of UPA) if the delayed application or detachment occurred within the first week of patch use and unprotected sexual intercourse occurred in the previous 5 days.
• Emergency contraception may also be considered (with the exception of UPA) at other times as appropriate.

Figure 3. Recommended actions after delayed application or detachment with combined hormonal patch.

[a]If detachment takes place but the woman is unsure when detachment occurred, consider the patch to have been detached for 48 hours or more because a patch should have been applied or reattached.

UPA = ulipristal acetate

Source: CDC. Note: Reference to specific commercial products, manufacturers, companies, or trademarks does not constitute its endorsement or recommendation by the U.S. Government, Department of Health and Human Services, or Centers for Disease Control and Prevention. This material is otherwise available on the agency website for no charge.

e. Advantages and disadvantages (Table 16)

Table 16. Advantages and Disadvantages of Transdermal Contraception Patch

Advantages	Disadvantages
Efficacy Adherence User controlled Readily reversible	Site reactions Patch detachment Cost Appearance, less privacy Breast discomfort Dysmenorrhea Headache Nausea Should not be used in women > 90 kg Questionable increased risk of blood clots

3. Vaginal rings
   a. NuvaRing; EluRyng (other AB-rated products may be available)
      i. Product inserted vaginally; delivers 15 mcg ethinyl estradiol and 120 mcg etonogestrel (active form of desogestrel) daily.
      ii. Effectiveness: Similar to pills (7% failure rate for typical use, 0.3% for perfect use) (Contraceptive Technology, 21st ed. New York: Ardent Media, 2018)
      iii. Adherence
         (a) One study found that 92.4% of women using a vaginal ring were adherent versus 75.4% using the COC pill.
         (b) Users were 96% satisfied; 97% would recommend the ring.
      iv. Counseling
         (a) Proper use
            (1) Insert vaginal ring into vagina and leave for 3 weeks. Week 4, remove and dispose ring and menses will occur.
            (2) Should not be removed during intercourse.
            (3) May be worn with tampon if there is breakthrough bleeding.
         (b) Missed doses: Inadvertent removal, expulsion, or prolonged ring-free interval
            (1) If 3 hours or less, rinse with cool to lukewarm water and reinsert as soon as possible.
            (2) If more than 3 hours, reinsert and use a BUM until ring has been used continuously for 7 days.
         (c) Alternative recommendations for missed vaginal ring insertion (MMWR Recomm Rep 2016;65:1-66)

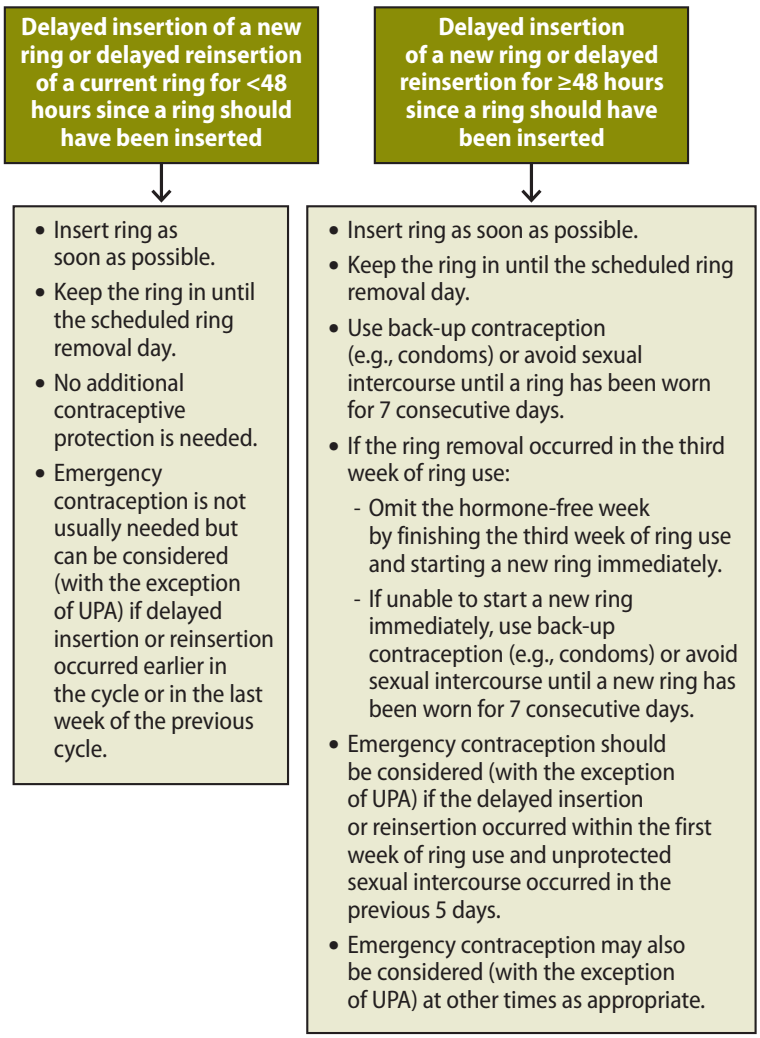

Delayed insertion of a new ring or delayed reinsertion of a current ring for <48 hours since a ring should have been inserted
• Insert ring as soon as possible.
• Keep the ring in until the scheduled ring removal day.
• No additional contraceptive protection is needed.
• Emergency contraception is not usually needed but can be considered (with the exception of UPA) if delayed insertion or reinsertion occurred earlier in the cycle or in the last week of the previous cycle.
Delayed insertion of a new ring or delayed reinsertion for ≥48 hours since a ring should have been inserted
• Insert ring as soon as possible.
• Keep the ring in until the scheduled ring removal day.
• Use back-up contraception (e.g., condoms) or avoid sexual intercourse until a ring has been worn for 7 consecutive days.
• If the ring removal occurred in the third week of ring use:
- Omit the hormone-free week by finishing the third week of ring use and starting a new ring immediately.
- If unable to start a new ring immediately, use back-up contraception (e.g., condoms) or avoid sexual intercourse until a new ring has been worn for 7 consecutive days.
• Emergency contraception should be considered (with the exception of UPA) if the delayed insertion or reinsertion occurred within the first week of ring use and unprotected sexual intercourse occurred in the previous 5 days.
• Emergency contraception may also be considered (with the exception of UPA) at other times as appropriate.

Figure 4. Recommended actions after delayed insertion or reinsertion with combined vaginal ring.

[a]If removal takes place but the woman is unsure of how long the ring has been removed, consider the ring to have been removed for 48 hours or more because a ring should have been inserted or reinserted.

UPA = ulipristal acetate

Source: CDC. Note: Reference to specific commercial products, manufacturers, companies, or trademarks does not constitute its endorsement or recommendation by the U.S. Government, Department of Health and Human Services, or Centers for Disease Control and Prevention. This material is otherwise available on the agency website for no charge.

(d) Adverse effects
(1) Decreased libido (8%)
(2) Breast tenderness (4%)
(3) Device-related events (2.5%–5%)
(4) Vaginal discomfort and secretions (2.5%)
(5) Irregular bleeding (1.5%–5%)

v. Advantages and disadvantages (Table 17)

b. Annovera
i. Product inserted vaginally, delivers 0.15 mg/day of segesterone and 13 mcg/day of ethinyl estradiol

ii. Effectiveness: 96%–98% effective in preventing pregnancy, has not been studied in women with a BMI greater than 29 kg/m^2
iii. Counseling:
  (a) Proper use
    (1) Insert vaginal ring into vagina and leave for 3 weeks. Week 4, remove and keep ring and menses will occur. Ring is washed with mild soap and lukewarm water, dried, and stored in the case provided. The same ring is reinserted after 7 days.
    (2) Should not be removed during intercourse
    (3) The same vaginal ring is used for 13 cycles (1 year)
    (4) Does not need to be stored in the refrigerator
  (b) Missed doses:
    (1) If out 2 hours or less, rinse with warm water and reinsert as soon as possible
    (2) If out 2 hours or more at one time or out for a time that adds up to more than 2 hours over the 21 days, a backup contraceptive method should be used until the ring has been in place continuously for 7 days
  (c) Adverse effects (greater than 5%)
    (1) Headache/migraine
    (2) Nausea/vomiting/diarrhea
    (3) Abdominal pain
    (4) Yeast infections
    (5) Dysmenorrhea
    (6) Vaginal discharge
    (7) Breast tenderness
    (8) Menstrual irregularities
    (9) Urinary tract infections
    (10) Genital itching
  (d) Drug interactions
    (1) Similar to those with combined hormonal contraceptives
    (2) Increased exposure to hormones occurs with oil-based suppositories such as miconazole 1- or 3-day treatments. Only water-based suppositories should be used concurrently with this vaginal ring.
  (e) Contraindications – Similar to combined hormonal contraceptives

Table 17. Advantages and Disadvantages of Contraceptive Vaginal Ring

Advantages	Disadvantages
Efficacy Adherence User controlled Cycle control Readily reversible Privacy	Adverse effects similar to other combined regimens Vaginal discomfort Potential partner awareness of ring

4. Extended regimens
  a. 3 months: Using active form of combined hormonal contraception for 3 months (results in menses every 3 months instead of once a month)
  b. 1 year: Using active form of combined hormonal contraception for 1 year
  c. Recommendations may be available for use of other nonlabeled products in an extended dosing regimen.

VIII. PROGESTIN-ONLY CONTRACEPTIVES

A. Indications: Those who cannot use or tolerate combined hormonal contraceptives (see list) or those seeking long-term contraception
   1. History of or current MI, stroke, DVT, CVD
   2. Atrial fibrillation
   3. Blood pressure 160/100 mm Hg
   4. Smoker age 35 or older
   5. Active, symptomatic liver disease
   6. Migraine headache with neurologic impairment or aura
   7. Retinopathy or neuropathy because of diabetes
   8. Surgery within the past 4 weeks
   9. Breastfeeding (estrogen may decrease breastmilk production)

B. Components: One of the following progestins
   1. Norethindrone
   2. Norgestrel
   3. Drospirenone
   4. Depot medroxyprogesterone acetate (DMPA)

C. Mechanisms of Action
   1. Thickens cervical mucus, prevents sperm movement.
   2. Thins uterus lining.
   3. Suppresses midcycle peak of LH and FSH, inhibits ovulation (minimal with oral progestin pills).

D. Contraindications
   1. Suspected or demonstrated pregnancy
   2. Active hepatitis, hepatic failure, jaundice
   3. Inability to absorb sex steroids from GI tract (i.e., active colitis)
   4. Concurrently taking medications that increase hepatic clearance (CYP inducers). Note: Medroxyprogesterone acetate okay to use with CYP inducers.
   5. Taking an antibiotic such as rifampin or rifabutin (category 3), broad-spectrum antibiotics (category 1).

E. Adverse Effects: See progestin adverse effects in Combined Hormonal Contraceptives section earlier in text.

F. Types
   1. Oral—progestin-only pills (POPs)
      a. Norethindrone 0.35 mg ("mini-pill," prescription only) or norgestrel 0.075 mg daily (OTC)
         i. Effectiveness: 7% failure rate (typical), 0.3% failure (perfect use) (Contraceptive Technology, 21st ed. New York: Ardent Media, 2018)
         ii. Start methods: May start on any day or on first day of period. There are no hormone-free days.
         iii. Adverse effects: Progestin related (see earlier text)
         iv. Missed doses: Doses must be at the SAME time every day; a missed dose means more than 3 hours late to take a dose. If a missed dose occurs, must use a BUM for 48 hours.
         v. Advantages
            (a) Efficacy
            (b) Decreased menstrual blood loss, cramps, pain
            (c) Readily reversible

(d) Preferable in lactating women
(e) Norgestrel available as OTC (approved July 2023; available as of March 2024)

vi. Disadvantages
(a) Progestin-related adverse effects (e.g., weight gain, acne)
(b) Irregular menses
(c) Adherence: Short time window for a missed pill
(d) Low-dose progestin; patient may ovulate
(e) Fewer noncontraceptive benefits

b. Drospirenone 4 mg
i. Effectiveness: 98% effective in preventing pregnancy
ii. Start methods: Start active tablet on the first day of menses. There are 24 active tablets and 4 inactive tablets.
iii. Adverse effects: Acne, metrorrhagia, headache, breast pain or tenderness, weight gain, dysmenorrhea, nausea, vaginal hemorrhage, decreased libido, and irregular bleeding
iv. Missed doses: If 1 active tablet is missed, take as soon as possible and finish the pill pack as instructed. If 2 active tablets are missed, take the last missed tablet as soon as possible. Continue taking 1 tablet a day as instructed. Use an additional BUM for 7 days.
v. Advantages: Dosing is not as sensitive to timing as for traditional POPs.
vi. Disadvantages
(a) Progestin-related adverse effects
(b) Irregular menses
(c) Monitoring of thromboembolism, hyperkalemia, bone loss

2. Depot medroxyprogesterone acetate (DMPA) intramuscular (IM) injection
a. A 1-mL crystalline suspension of 150 mg of DMPA injected intramuscularly into deltoid or gluteus maximus muscle every 11–13 weeks
b. Effectiveness: Perfect use failure rate: 0.3%; typical use failure rate: 4% (Contraceptive Technology, 21st ed. New York: Ardent Media, 2018)
c. Start methods
i. Preferred start: First 5 days of menses. No BUM needed.
ii. Alternative start: Any time in cycle if not pregnant. Use BUM for 7 days.
iii. Postpartum: May give injection before hospital discharge.
iv. Breastfeeding: May start immediately or wait 4–6 weeks.
v. Switching methods: Any time patient known to be not pregnant. Use BUM if necessary.
d. Adverse effects
i. Progestin related (see earlier text)
ii. Progressive significant weight gain
iii. Severe depression (rare)
iv. Boxed warning: Loss of bone; women who used DMPA for at least 5 years have significantly reduced BMD of lumbar spine and femoral neck, particularly after 15 years of use and if initiated before age 20.
(a) The effect is almost completely reversible, even after 4 years or more of DMPA use.
(b) All women placed on DMPA should be taking sufficient calcium and exercising regularly.
e. Missed dose: More than 13 weeks between injections. Rule out pregnancy before providing next injection if more than 15 weeks since last dose.

f. Patient counseling
   i. Wait a few hours before massaging area where shot was given.
   ii. Irregular bleeding or spotting in the beginning that should decrease over time.
   iii. Take calcium if not achieving 1000–1200 mg/day through diet.
   iv. Return in 11–13 weeks for next injection. Use BUM if ever more than 13 weeks.
   v. If ever changing from DMPA to another method, start method when next injection is due.
   vi. May have delayed return to fertility for up to 18 months. Use with caution in women 35 years or older who express interest in future conception.

3. DMPA subcutaneously: Subcutaneous injection of 104 mg DMPA, information similar to that stated earlier but, in addition, has FDA indication for endometriosis.

IX. INTRAUTERINE DEVICES (IUDs)

A. Indications: To prevent pregnancy long term; levonorgestrel IUD is also indicated for heavy menses in women who elect to use an IUD for contraception.

B. Recommended for Women Who:
   1. Have no history of pelvic inflammatory disease (PID) or ectopic pregnancy
   2. Have heavy menses, cramps, anemia, or dysfunctional uterine bleeding
   3. Are seeking long-term (2 years or more) pregnancy protection
   4. Do not want to use estrogen-containing products

C. Types
   1. Copper (ParaGard T 380A)
      a. Copper IUD inserted into the uterus by a health care professional
      b. Mechanism of action
         i. Primary action: Spermicidal
         ii. Copper ions inhibit sperm motility and acrosomal enzyme activation so that sperm seldom reach fallopian tube and are unable to fertilize the ovum.
         iii. A sterile inflammatory reaction created in endometrium phagocytizes sperm.
         iv. Does not interfere with ovulation and is not an abortifacient.
      c. Effectiveness: Perfect use failure rate: 0.6%; typical use failure rate: 0.8% (Contraceptive Technology, 21st ed. New York: Ardent Media, 2018)
      d. Contraindications specific to copper IUD
         i. Pregnancy
         ii. Women with current or recent (within 3 months) sexually transmitted infection (STI) or woman at risk of STI
         iii. Uterus less than 6 cm or greater than 9 cm
         iv. Undiagnosed abnormal vaginal bleeding
         v. Active cervicitis or active pelvic infection
         vi. Known symptomatic actinomycosis
         vii. Recent endometritis (past 3 months)
         viii. Allergy to copper; Wilson's disease
         ix. Uterine distortion or pathology affecting placement
         x. Known or suspected uterine or cervical cancer
         xi. Unresolved abnormal Papanicolaou (Pap) test
         xii. Severe anemia (relative contraindication)

e. Advantages and disadvantages (Table 18)

Table 18. Advantages and Disadvantages of Copper IUD

Advantages	Disadvantages
Efficacy (long term, 10 yr)	Monthly blood loss increased about 35%
Adherence	Dysmenorrhea
Spontaneous sexual activity	Spotting and cramping
Readily reversible	Expulsion
Cost-effective	Foreign body
Patient satisfaction	Increased risk of infection for 20 days after insertion

IUD = intrauterine device.

2. Progestin (levonorgestrel)
   a. Kyleena: Inserted into uterus by health care professional, stays in for up to 5 years, releases 17.5 mcg levonorgestrel per day for the first year, then 9.8 mcg/day for the second year, and decreases to 7.4 mcg/day by the fifth year; indicated for contraception.
   b. Liletta: Inserted into uterus by a health care professional; stays in for up to 8 years; releases 18.6 mcg/day initially and declines steadily to 16.3 mcg/day at 1 year, 14.3 mcg/day at 2 years, 12.6 mcg/day at 3 years, and to about 8.6 mcg/day after 6 years; indicated for contraception.
   c. Mirena: Inserted into uterus by health care professional, stays in for up to 8 years, releases 20 mcg levonorgestrel per day for the first 5 years, 10 mcg/day during the sixth year, and about 8 mcg/day during the seventh year; indicated for contraception and menorrhagia.
   d. Skyla: Inserted into uterus by a health care professional; stays in for up to 3 years; releases 14 mcg levonorgestrel per day after 24 days, decreasing to 10 mcg/day after 60 days and then to less than 5 mcg after 3 years; indicated for contraception.
   e. Mechanism of action
      i. Foreign object in uterus, prevents implantation
      ii. Progestin thickens cervical mucus, thins endometrium, and inhibits sperm motion.
      iii. Effectiveness: 99% effective in preventing pregnancy
   f. Contraindications (package insert)
      i. Pregnancy or suspicion of pregnancy
      ii. Congenital or acquired uterine anomaly
      iii. Acute or history of PID
      iv. Postpartum endometritis or infected abortion in the past 3 months
      v. Known or suspected uterine or cervical neoplasia
      vi. Unresolved abnormal Papanicolaou (Pap) test
      vii. Genital bleeding of unknown etiology
      viii. Untreated acute cervicitis or vaginitis
      ix. Acute liver disease or liver tumor (benign or malignant)
      x. Woman or partner with several sexual partners
      xi. Conditions associated with increased susceptibility to infections with microorganisms (e.g., leukemia, acquired immunodeficiency syndrome, intravenous drug abuse)
      xii. Genital actinomycosis
      xiii. A previously inserted IUD that has not been removed
      xiv. Hypersensitivity to any component of this product
      xv. Known or suspected carcinoma of the breast
      xvi. History of ectopic pregnancy or condition that would predispose to ectopic pregnancy

g. Advantages and disadvantages (Table 19)

Table 19. Advantages and Disadvantages of Progestin IUD

Advantages	Disadvantages
Efficacy (long term, 3–8 yr) Adherence Menorrhagia improves Spontaneous sexual activity Readily reversible	Progestin-related adverse effects Irregular menses (generally for the first 6 mo; then possibly amenorrhea) Expulsion Increased risk of infection first 20 days after insertion Foreign body

IUD = intrauterine device.

D. Patient Counseling
   1. Strings of IUD will be outside the cervix. Patient will be instructed on how and when to check the strings to verify IUD is still inserted correctly.
   2. Adverse effects: PAINS
      a. **P:** Period late; abnormal spotting or bleeding
      b. **A:** Abdominal pain, pain with intercourse
      c. **I:** Infection exposure (STI); abnormal vaginal discharge
      d. **N:** Not feeling well, fever, chills
      e. **S:** String missing, shorter, or longer

X. IMPLANT (NEXPLANON)

A. Indication: Long-term prevention of pregnancy for up to 3 years

B. Components: Etonogestrel, releases 60–70 mcg/day during weeks 5–6 and then decreases to 35–45 mcg/day by the end of the first year, 30–40 mcg/day after the second year, and 25–30 mcg/day at the end of 3 years. Of note: etonogestrel (Implanon) has been discontinued; only etonogestrel (Nexplanon) is being manufactured and distributed currently.

C. Mechanism of Action: A rod inserted in upper arm, 99% effective for up to 3 years, releases progestin etonogestrel, which acts similarly to other progestin-only contraceptives; not tested in women weighing more than 130% of their ideal body weight; may be less effective in overweight women; return to fertility within 1–3 months; Nexplanon is radio-opaque so it is visible on radiograph.

D. Adverse Effects
   1. Similar to progestin-related adverse effects.
   2. Bleeding irregularities
   3. Site reactions, inflammation, hematoma, pain, redness at site (3.6%)
   4. Difficulty removing rod after 3 years, rod breaks, fibrosis (1.7%)

E. Studies (see Contraceptive CHOICE Project under IUD section)

XI. LACTIC ACID, CITRIC ACID, AND POTASSIUM BITARTRATE VAGINAL GEL (PHEXXI)

A. Single use applicator inserted into the vagina before sex

B. Lowers pH of the vagina and decreases the motility or mobility of the sperm. It is not a spermicide.

C. Must be used before each session of sex ("1 dose, 1 hour, 1 act").

D. 86–93% effective

E. Can be used in combination with other methods, except for the vaginal ring.

F. Benefits: Hormone free, potential for increased sexual satisfaction

G. Adverse effects: Vaginal irritation (increased risk with increased frequency of use)

XII. EMERGENCY CONTRACEPTION

A. Definition: "A therapy used to prevent pregnancy after an unprotected or inadequately protected act of sexual intercourse." ACOG definition (ACOG Practice Bulletin 152. Obstet Gynecol 2015;126:e1-11)

B. Mechanism of Hormonal Methods
   1. Inhibits ovulation
   2. Prevents fertilization
   3. Increases thickness of cervical mucus
   4. Prevents implantation (controversial; most recent data suggest this does not occur)
   5. Not considered an abortifacient by medical standards; does not disrupt an implanted, fertilized egg.

C. Indications
   1. Unprotected or inadequately protected vaginal intercourse
   2. Misused contraceptive method (e.g., missed a pill, contraceptive patch fell off)
   3. Sexual assault
   4. Exposure to teratogen

D. Timing: Within 120 hours after unprotected intercourse; package insert for marketed products (levonorgestrel products) states 72 hours, but studies show up to 120 hours may still prevent pregnancy.

E. Effectiveness: 57%–85%

F. Methods
   1. Progestin-only method
      a. Levonorgestrel 1.5 mg (1 tablet)
      b. Available OTC for all ages; anyone may purchase.
      c. Adverse effects
         i. Nausea: 18%; vomiting: 4%
         ii. May notice changes in menstrual cycle

2. Ulipristal acetate 30 mg (1 tablet)
    a. Prescription only
    b. Progesterone receptor modulator: Binds to progesterone receptor
    c. Indicated for EC within 120 hours of unprotected intercourse; reported to have 42% more effectiveness in preventing pregnancy than levonorgestrel at 72 hours postcoitus
    d. Adverse effects: Headache, nausea, abdominal pain, dysmenorrhea, menstrual changes
    e. Not approved for use during breastfeeding
    f. Recommended to wait 5 days before initiating or resuming hormonal contraception after taking ulipristal. Starting hormonal contraception before waiting 5 days might alter the effect of ulipristal as well as the effect of hormonal contraception.
3. Copper IUD: May be used within 5 days of unprotected intercourse; requires in-office visit.
4. Levonorgestrel IUD: Shown to be noninferior to copper IUD at preventing pregnancy when inserted within 120 hours of unprotected vaginal intercourse (N Engl J Med 2021;384:335-44).
5. Yuzpe method (not frequently utilized clinically)
    a. High-dose estrogen plus progestin with dosing obtained using available COC products.
    b. Adverse effects
        i. Nausea: 30%–60%; vomiting: 33% with estrogen-containing EC (if vomiting within 2 hours of dose, repeat dose; may take with food or meclizine 50 mg prophylactically 30–60 minutes before each dose)
        ii. May notice changes in menstrual cycle
        iii. Breast tenderness, headache

G. Special Populations
1. BMI greater than 25 kg/m^2
    a. Progestin-only emergency contraceptive pills are not as effective for those with a BMI of 25 kg/m^2 or greater. Either ulipristal acetate (ella) or the copper IUD (Paragard T380A) is recommended for these patients. CDC Medical Eligibility criteria state that hormonal methods of EC may lose effectiveness at a BMI of 30 kg/m^2 and higher.
    b. Controversial: Because of conflicting and limited data, FDA states that a definitive conclusion is not yet possible regarding the efficacy of levonorgestrel EC in patients with BMI greater than 25 kg/m^2; therefore, no change in labeling is currently warranted (www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/plan-b-consumer-questions-and-answers).
    c. The copper IUD is recommended for those with a BMI greater than 35 kg/m^2.
2. Breast/chestfeeding people: All EC methods are category 1 for use according to the CDC Medical Eligibility Criteria; exception: breast/chestfeeding not recommended within 24 hours of taking ulipristal because of high concentrations of ulipristal in milk during first 24 hours, with the highest peak 1–3 hours after administration (breast milk for first 24 hours after administration should be discarded)

Patient Case

7. A person is seeking over the counter (OTC) emergency contraception (EC). It has been 68 hours since unprotected vaginal intercourse. They usually use the injectable depot medroxyprogesterone acetate injection (last dose 16 weeks ago). The person has a body mass index (BMI) of 28 kg/m^2. Which counseling point is most appropriate for this person regarding use of OTC EC?

    A. OTC EC is most effective the sooner it is taken, but can be taken up to 120 hours after unprotected vaginal intercourse.

    B. OTC EC should not be used in patients prescribed another form of hormonal contraception.

    C. OTC EC will not work for people with a BMI greater than 25 kg/m^2.

    D. OTC EC is not associated with any side effects.

XIII. MENSTRUAL DISORDERS (Independent Study)

A. Amenorrhea
   1. Definitions
      a. Primary: Absence of menarche by age 16 years with presence of secondary development or age 14 years with absence of secondary development and absence of menarche
      b. Secondary: Absence of menses for 6 months or three cycles (more common than primary)
   2. Causes
      a. Rule out pregnancy.
      b. Excessive exercise or low BMI
      c. Hyperprolactinemia
      d. PCOS
      e. Unknown
   3. Treatment
      a. Excessive exercise or low BMI
         i. Decrease exercise and encourage weight gain.
         ii. Combined hormonal contraceptives
         iii. Estrogen therapy
            (a) Conjugated estrogens 0.625 to 1.25 mg orally daily on cycle days 1–25
            (b) Transdermal ethinyl estradiol 50 mcg/day patch
      b. Hyperprolactinemia
         i. Bromocriptine 2.5 mg orally daily
         ii. Cabergoline 0.25 mg orally twice weekly; then increase as needed.
      c. PCOS (see Endocrine and Metabolic Disorders chapter)
      d. Unknown primary
         i. Combined hormonal contraceptives
         ii. Estrogen therapy
            (a) Conjugated estrogens 0.625 to 1.25 mg orally daily on cycle days 1–25
            (b) Transdermal ethinyl estradiol 50 mcg/day patch
      e. Unknown secondary
         i. Progestins
            (a) Micronized progesterone 400 mg orally daily for 10 sequential days to induce menses
            (b) Medroxyprogesterone acetate 5 to 10 mg orally daily on days 14–25 to induce menses
         ii. Combined hormonal contraceptives

B. Abnormal Uterine Bleeding
   1. Definition: "Bleeding from the uterine corpus that is abnormal in regularity, volume, frequency or duration in the absence of pregnancy." (ACOG Committee Opinion No. 557 April 2013)
   2. Causes
      a. Structural: "PALM"
         i. **P**olyp
         ii. **A**denomyosis
         iii. **L**eiomyoma
         iv. **M**alignancy and hyperplasia
      b. Nonstructural: "COEIN"
         i. **C**oagulopathy
         ii. **O**vulatory dysfunction
         iii. **E**ndometrial
         iv. **I**atrogenic
         v. **N**ot yet classified

3. Assessment
    a. Initial laboratory testing
        i. Complete blood cell count
        ii. Blood type and cross-match
        iii. Pregnancy test
    b. Check for disorders of hemostasis
        i. PTT, PT, aPTT
        ii. Fibrinogen
        iii. Markers for von Willebrand disease
    c. Other laboratory tests
        i. Thyroid-stimulating hormone
        ii. Iron concentrations
        iii. Liver function tests
        iv. *Chlamydia trachomatis*
4. Treatment: Goal is to control current episode of heavy bleeding and reduce menstrual loss in subsequent cycles.
    a. Acute
        i. Hormonal therapy: First line
            (a) Progestins: Medroxyprogesterone acetate 20 mg orally three times daily for 7 days (for acute bleeding)
            (b) Estrogens: Intravenous conjugated equine estrogens
            (c) Combined hormonal contraceptives: Best if at least 35 mcg of ethinyl estradiol and monophasic; Estradiol valerate and dienogest (Natazia) has approved indication for heavy menstrual bleeding.
        ii. Tranexamic acid
        iii. Desmopressin (use with caution; may help for those with von Willebrand disease)
        iv. Surgery
            (a) Hysterectomy
            (b) Endometrial ablation (not recommended as primary therapy)
    b. Chronic
        i. Hormonal therapy: First line
            (a) Progestins
                (1) Medroxyprogesterone acetate 5–10 mg orally for 5–10 days starting on day 16 or day 21 of a 28-day cycle
                (2) Levonorgestrel IUD
            (b) Combined hormonal contraceptives: Low dose may be option.
        ii. Surgery
            (a) Hysterectomy
            (b) Endometrial ablation (not recommended as primary therapy)

C. Dysmenorrhea
1. Definition: Painful menses, usually cramping right before or during menses
2. Causes
    a. Primary: Caused by menstrual period, mediated by prostaglandins
    b. Secondary: Caused by disorder in reproductive system (endometriosis, fibroids, adenomyosis), usually starts later in life.

3. Treatment
    a. NSAIDs: Begin 1–2 days before menses
    b. Hormonal contraceptives: Combined hormonal contraceptives or levonorgestrel IUD
    c. Nonpharmacologic approaches (exercise, heat therapy, self-acupressure, acupuncture)

D. Endometriosis
1. Definition: Chronic disorder that may result in chronic pain and infertility, endometrial tissue found outside the uterus
2. Treatment
    a. Hormonal contraceptives
        i. Combined hormonal contraceptives (not FDA-approved use; effective for dyspareunia, dysmenorrhea, and non-menstrual pain)
        ii. Depot medroxyprogesterone acetate (subcutaneous formulation, FDA-approved use)
        iii. Other progestin only options (pills, implant, IUD—not FDA approved use)
    b. Gonadotropin-releasing hormone (GnRH) agonists: Goserelin, leuprolide, nafarelin, triptorelin; recommended as second line because of adverse effect profile
        i. Consider adverse effects such as osteopenia, hot flashes, vaginal dryness.
        ii. Recommend calcium 1000 mg orally daily while taking GnRH agonist.
        iii. May use add-back therapy with norethindrone with or without low-dose conjugated estrogen; transdermal patch with estradiol and medroxyprogesterone acetate may also be used if norethindrone is not well tolerated.
        iv. See GnRH analog drug information in the Infertility section that follows.
    c. GnRH antagonists: Elagolix (Orilissa) - Approved for the treatment of moderate to severe pain associated with endometriosis and endometriosis with dyspareunia (N Engl J Med 2017;377:28-40); recommended as second line
        i. Endometriosis dose - 150 mg orally once daily, maximum use 24 months
        ii. Endometriosis with dyspareunia - 200 mg orally twice daily, maximum use 6 months
        iii. For moderate hepatic impairment, the dose is 150 mg orally once daily for a maximum of 6 months.
        iv. Adverse effects: Bone loss, mood changes, elevated liver function enzymes
        v. Contraindications: Pregnancy, severe osteoporosis, severe hepatic impairment, use of strong organic anion transporting polypeptide 1B1 inhibitors; may decrease effect of estrogen-containing contraceptives (best to use non-hormonal method of contraception during treatment as well as for 7 days after treatment with elagolix)
    d. Danazol
        i. Androgenic agent that should be reserved for those without access to other treatment options.
        ii. Adverse effects: Acne, hirsutism, myalgias
    e. Aromatase inhibitors: Anastrozole or letrozole, need hormonal contraceptive in addition to minimize risk of ovarian stimulation; reserve for refractory treatment.
    f. NSAIDs
        i. Used to help decrease pain
        ii. Ibuprofen and naproxen
    g. Surgery

E. PCOS (see Chapter, “Endocrine and Metabolic Disorders”)

XIV. INFERTILITY

A. Background
   1. Using no birth control method, women have an 85% chance of pregnancy over 1 year.
   2. About 20% of women have their first baby after age 35.
   3. Probability of having a baby decreases 3%–5% every year after age 30; faster after age 40.
   4. Miscarriages: 12%–15% for those in their 20s, 50% after age 40
   5. Fertility improves with BMI of 20–25 kg/m^2 or within 15% of ideal body weight; fertility decreased in those less than 95% of ideal body weight or in those greater than 125% of ideal body weight.

B. Definition
   1. Unprotected intercourse for 1 year that has not resulted in conception
   2. The woman is 35 years of age or older, is having unprotected intercourse, and has not conceived within 6 months

C. Risk Factors
   1. Age older than 35 years
   2. Tobacco use
   3. Alcohol use
   4. Caffeine use (more than 500 mg/day)
   5. Vitamin D deficiency
   6. Excessive exercise
   7. BMI less than 19 kg/m^2 or more than 25 kg/m^2 for women

D. Causes of Infertility
   1. Male factor
      a. Endocrine: Spermatogenesis, hypogonadism
      b. Anatomic: Blockage, abnormal anatomy
      c. Sexual dysfunction: Ejaculation or erection difficulties
      d. Often treated with sperm extraction and assisted reproductive technologies
   2. Female factor
      a. Ovulatory
         i. WHO group I: Hypogonadotropic hypogonadal anovulation
            (a) About 5%–10% of anovulatory women
            (b) Low estrogen, low FSH
         ii. WHO group II: Eugonadotropic anovulation (normogonadotropic normoestrogenic anovulation)
            (a) About 75%–85% of anovulatory women
            (b) Normal FSH concentrations
            (c) Women with PCOS generally fall into this classification.
         iii. WHO group III: Hypergonadotropic anovulation
            (a) About 10%–20% of anovulatory women
            (b) Elevated FSH concentrations
            (c) Premature ovarian failure or advanced age fall into this classification.
         iv. Hyperprolactinemic anovulation
            (a) About 5%–10% of anovulatory women
            (b) May have hyperprolactinemia.
            (c) Laboratory values may appear similar to those in WHO group I.

b. Cervical
    i. Abnormality
    ii. Blockage
    iii. Thickened cervical mucus
c. Pelvic
    i. Fibroids
    ii. Endometriosis
    iii. Fallopian tube damage or blockage
    iv. Uterine abnormality
    v. Pelvic adhesions

E. Medical Conditions in Women
1. PCOS
2. Endometriosis
3. Pelvic inflammatory disease
4. Uterine fibroids
5. Idiopathic

F. Fertility Agents
1. Clomiphene citrate
    a. Used to stimulate or induce ovulation (used off-label to increase sperm production in men)
    b. Administered for 5 days starting on days 2, 3, 4, or 5 of cycle
    c. Taken by mouth usually 50–150 mg/day
    d. First-line agent, often not effective in WHO group 1 or 3 ovulation disorders
    e. Selective estrogen receptor modulator that works by blocking estrogen receptors; body perceives hypoestrogenic state and increases the release of GnRH, which increases concentrations of FSH and LH.
    f. Adverse effects: Hot flashes, abdominal and breast tenderness, mood swings, visual alterations
2. Aromatase inhibitors (off-label use): letrozole, anastrozole
    a. Increase GnRH and gonadotropins, used in anovulatory WHO group 2 patients
    b. Help induce ovulation with less risk of multiple follicles stimulated (less risk of multiple births).
    c. Adverse effects: Headache, GI complaints, joint pain, bone pain, edema, sweating, and flushing
3. Human menopausal gonadotropin (hMG)
    a. Class known as menotropins, both FSH and LH
    b. Derived from the urine of postmenopausal women
    c. Given on day 2 or 3 of cycle and continued for 7–10 days, or as determined by estradiol concentrations and ultrasound monitoring of follicle development.
    d. Regimens may vary for in vitro protocols.
    e. Adverse effects: Flu-like symptoms, muscle aches, malaise, headaches, dizziness, pain at site
4. Follicle-stimulating hormone (FSH)
    a. Naturally occurring (urine source): Bravelle urofollitropin
    b. Recombinant: follitropin alpha, follitropin beta
    c. Injection form
    d. Highly purified
    e. Helps stimulate development of follicle in ovary; given in the first half of the cycle.
    f. Adverse effects: Mood swings, depression, breast tenderness and swelling, pain at site

5. Human chorionic gonadotropin (hCG)
    a. Recombinant: Ovidrel injection subcutaneously
    b. Naturally occurring: Derived from urine of pregnant women, Pregnyl or Novarel, injection intramuscularly
    c. Similar to LH.
    d. Helps stimulate release of egg; given 36 hours before insemination or harvest.
    e. Adverse effects: Irritation at site of injection, edema, headache, mood changes, thromboembolic disorder, allergic reactions
6. GnRH analogs
    a. Used to prevent LH surge that occurs right before ovulation, which helps with timing of ovulation.
    b. Helps optimize the effectiveness of hMG or FSH.
    c. Administered by nasal spray, injection, or capsule
    d. Also used to treat endometriosis.
    e. Induces "menopause" state; may cause osteoporosis in women who use agents for long periods; not usually the case in infertility treatment, but more so for endometriosis.
    f. Agonists versus antagonists
        i. GnRH agonists
            (a) Leuprolide, nafarelin
            (b) Adverse effects: Hot flashes, headache, mood swings, insomnia, vaginal dryness, decreased breast size, bone loss
        ii. GnRH antagonists
            (a) Ganirelix and cetrorelix
            (b) More recently investigated for infertility protocols versus traditional use of GnRH agonists.
            (c) Said to have fewer complications.
            (d) Faster onset of action than agonists
7. Metformin
    a. Sometimes used in conjunction with clomiphene to help ovulation in women with PCOS.
    b. Increases insulin sensitivity and decreases hyperinsulinemia, thus reducing circulating androgens.
    c. Weight loss may also occur, leading to better outcomes for ovulation.

G. Other Fertility Agents
1. Progesterone: Used for luteal phase support or patients with frequent miscarriages
    a. Capsules (micronized): Orally, vaginally
    b. Injectables
    c. Vaginal suppositories
2. Bromocriptine: Decreases prolactin concentrations; prolactin lowers progesterone concentrations, may prevent ovulation.
3. Sildenafil: Aids in increasing the thickness of uterus lining (off-label use).
4. Guaifenesin: May help thin the cervical mucus to aid in conception (off-label use).
5. Aspirin: Can be used before fertility procedures for uterine blood flow and decreased risk of ovarian hyperstimulation syndrome.

H. Complications: Ovarian Hyperstimulation Syndrome
1. Etiology
    a. Life-threatening complication of assisted conception
    b. Occurs in less than 4% of cycles for ovulation induction.
    c. About 1%–10% for in vitro fertilization
    d. Usually occurs in postovulatory stage.

2. Pathophysiology
    a. Ovary enlargement
    b. Capillary permeability increase
    c. Protein-rich fluid escaping from the intravascular space to the extravascular space
    d. Patient may start to feel bloated; shortness of breath may occur; lethargy, nausea, vomiting, and diarrhea.
3. Clinical signs
    a. Rapid weight gain
    b. Ascites
    c. Pleural and pericardial effusions
    d. Oliguria or anuria
    e. Hemoconcentration
    f. Leukocytosis
    g. Hypovolemia, hyponatremia, hyperkalemia
    h. Adult respiratory distress syndrome
    i. Hypercoagulability
    j. Multiple organ failure
4. Risk factors
    a. Young age
    b. Low body weight
    c. High estradiol concentrations or rapidly increasing
    d. Size and number of follicles stimulated
    e. Number of eggs retrieved
    f. History of PCOS
5. Outpatient management
    a. Light physical activity
    b. Drink 1 L of fluid a day.
    c. Possibly withhold hCG injection to prevent it.
6. Hospital management
    a. Fluid management
    b. Thrombosis prophylaxis

Patient Case

8. A 37-year-old woman (BMI 26.3 kg/m^2) has unsuccessfully been trying to conceive for the past 12 months. She and her partner engage in unprotected intercourse. She denies tobacco and alcohol use. Her medical history is significant for polycystic ovarian syndrome (PCOS). She has been treated with clomiphene 100 mg/day for 5 days (starting on day 3 of her menstrual cycle) for the past 3 months without success. Which would be the next best step for treating her infertility?

    A. Continue clomiphene; add metformin.

    B. Discontinue clomiphene; add metformin.

    C. Continue clomiphene; add human chorionic gonadotropin (hCG).

    D. Discontinue clomiphene; add hCG.

XV. SEXUALLY TRANSMITTED INFECTIONS

A. Herpes Simplex Virus (HSV) Infection
   1. Characteristics
      a. Types: Genital herpes is caused by HSV; predominantly HSV-2 and, to a lesser extent, HSV-1.
      b. Diagnosed in in more than 500,000 individuals each year in the United States, with 11.9% of persons aged 14–49 years estimated to be infected.
      c. Treatment can partly control symptoms but does not affect the risk, frequency, or severity of recurrences after it is discontinued.
      d. Symptoms include itching, genital burning, vesicle formation, and ulcer formation. Most persons infected with HSV-2 have mild or unrecognized infections but shed virus intermittently in the anogentical area.
      e. After the primary infection, the virus is latent in the sacral dorsal root ganglia.
      f. From 50% to 80% of patients have recurrent infections (generally less severe and of shorter duration).
   2. Diagnosis
      a. Culture and polymerase chain reaction: Preferred
      b. Serologic testing
   3. Therapy
      a. First-episode primary HSV infection; treat for 7–10 days (can extend treatment time if healing is incomplete)
         i. Acyclovir 400 mg orally three times daily
         ii. Famciclovir 250 mg orally three times daily
         iii. Valacyclovir 1 g orally twice daily
      b. Recurrent HSV infection
         i. The regimens listed in recurrent and suppressive section are primarily for HSV-2 type, not for HSV-1. No data are available regarding the efficacy of suppressive therapy for preventing transmission among persons with HSV-1.
         ii. Optimal episodic treatment requires initiation of therapy as soon as prodromal symptoms present or within 1 day of lesion onset.
            (a) Acyclovir 800 mg orally three times daily for 2 days
            (b) Acyclovir 800 mg orally twice daily for 5 days
            (c) Famciclovir 125 mg orally twice daily for 5 days
            (d) Famciclovir 500 mg orally for 1 day; then 250 mg orally twice daily for 2 days
            (e) Famciclovir 1000 mg orally twice daily for 1 day
            (f) Valacyclovir 500 mg orally twice daily for 3 days
            (g) Valacyclovir 1000 mg orally once daily for 5 days
         iii. Daily suppressive therapy recommended in patients with six or more episodes yearly (reassess annually the need for suppressive therapy)
            (a) Acyclovir 400 mg orally twice daily
            (b) Famciclovir 250 mg orally twice daily
            (c) Valacyclovir 500 mg/day orally (may be less effective in those who have frequent recurrences [10+ episodes/year])
            (d) Valacyclovir 1000 mg/day orally
      c. Severe disease (e.g. disseminated infection, pneumonitis, or hepatitis)
         i. Should be hospitalized.
         ii. Treatment: Acyclovir intravenously 5–10 mg/kg every 8 hours for 2–7 days, followed by oral antiviral therapy for at least 10 days of total therapy

4. Herpes encephalitis
    a. Characteristics
        i. Caused primarily by HSV-1
        ii. Spreads through neural routes during primary or recurrent infection
        iii. Primarily temporal lobe involvement with eventual hemorrhagic encephalitis
        iv. Frequent neurologic sequelae, and high mortality if untreated
    b. Diagnosis
        i. Signs and symptoms (nonspecific)
            (a) Headache
            (b) Fever
            (c) Speech disorders and behavioral changes
            (d) Focal seizures
        ii. Cerebrospinal fluid analysis
            (a) Moderate pleocytosis (generally lymphocytosis)
            (b) Normal glucose and moderately elevated protein
        iii. Brain biopsy (rarely performed)
    c. Therapy: Treatment should be intravenous acyclovir for 21 days.
    d. According to the 2021 STI guidelines, HSV-2 meningitis is also a rare complication of HSV-2 genital herpes infection. The clinical characteristics and diagnosis are similar to herpes encephalitis; however, the treatment regimen is intravenous acyclovir until clinical improvement followed by high-dose oral antiviral therapy to complete 10–14 days course of therapy.

Patient Case

9. A 32-year-old man presents with reports of penile discharge and dysuria. He is given a diagnosis of a gonococcal infection. He has an allergy to penicillin (rash) and weighs 105 kg. Which treatment is most appropriate?

    A. Gentamicin 240 mg intramuscularly × 1 and azithromycin 2 g orally × 1.

    B. Tetracycline 500 mg orally four times per day × 28 days.

    C. Ceftriaxone 1000 mg intramuscularly × 1 and azithromycin 1 g orally × 1.

    D. Ceftriaxone 500 mg intramuscularly × 1 and doxycycline 100 mg orally twice per day × 7 days.

B. Syphilis (*Treponema pallidum*)
    1. Characteristics
        a. A systemic infection caused by *T. pallidum*, a spirochete bacterium that is transmitted primarily through sexual activity or during pregnancy
        b. Untreated syphilis in pregnant women can lead to fetal demise and congenital infection. Cases of congenital syphilis have recently increased in the United States.
        c. Persons who acquire *T. pallidum* remain chronically infected and can develop an array of clinical manifestations, which can progress in different stages (primary, secondary, latent, tertiary), with episodes of active clinical disease interrupted by periods of latent infection.
        d. Jarisch-Herxheimer reaction after initiating syphilis treatment
            i. Self-limited systemic reaction that typically begins within 4 hours after receiving the first antibiotic dose to treat syphilis, peaks in about 8 hours, and gradually resolves within 24 hours.
            ii. It results from transient release of inflammatory cytokines in response to spirochete lipoproteins lysed by antimicrobial therapy.
            iii. Most common symptoms associated with the Jarisch-Herxheimer reaction include fever, chills, tachycardia, myalgias, vasodilatation with flushing, accentuation of skin rash (if present pre-treatment), and dizziness (from mild to moderate hypotension).

iv. Management consists of supportive therapy with antipyretics and intravenous fluids (if needed). Premedicating with antipyretics or corticosteroids before an antimicrobial dose does not prevent the Jarisch-Herxheimer reaction.

2. Diagnosis
   a. Dark-field examination and direct fluorescent antibody stains of exudate for spirochetes
   b. Nontreponemal (Venereal Disease Research Laboratory and Rapid Plasma Reagin); detect serum concentrations of antibody to cardiolipin.
   c. Treponemal (fluorescent treponemal antibodies and *T. pallidum* particle agglutination test): Detect antibodies to *T. pallidum*.
   d. Two testing algorithms may be used
      i. Traditional testing algorithm: Nontreponemal test, confirm with the treponemal test.
      ii. Reverse testing algorithm: Treponemal test; if positive, followed by quantitative nontreponemal, then confirm with treponemal test if nontreponemal is negative.
3. Primary syphilis
   a. From 10 to 90 days after exposure (mean 21 days)
   b. The primary symptom is the development of a chancre.
   c. The chancre resolves spontaneously in 2–6 weeks, even without treatment.
   d. Recommended treatment
      i. Benzathine penicillin G 2.4 million units intramuscularly in a single dose (adults)
      ii. If penicillin allergy: Doxycycline 100 mg orally twice daily, tetracycline 500 mg four times daily for 2 weeks, or ceftriaxone 1 g intramuscularly or intravenously daily for 10 days (if tolerated). If pregnant, avoid doxycycline or tetracycline, and consider ceftriaxone if there is supporting efficacy data or low concern for cross-reactivity; otherwise, consider penicillin desensitization.
4. Secondary syphilis or early latent syphilis (<1 year)
   a. 4–10 weeks after exposure
   b. Skin lesions: Characteristically on the palms and soles
   c. Latent phase begins when all symptoms have resolved.
   d. Recommended treatment
      i. Benzathine penicillin G 2.4 million units intramuscularly in a single dose
      ii. If penicillin allergy: Doxycycline 100 mg orally twice daily, tetracycline 500 mg four times daily for 28 days, or ceftriaxone 1 g intramuscularly or intravenously daily for 10 days (if tolerated). If pregnant, avoid doxycycline or tetracycline, and consider ceftriaxone if there is supporting efficacy data or low concern for cross-reactivity; otherwise, consider penicillin desensitization.
5. Late latent syphilis
   a. More than 1 year in duration or unknown duration
   b. Recommended treatment
      i. Benzathine penicillin G 2.4 million units intramuscularly every week for 3 weeks
      ii. If penicillin allergy: Doxycycline 100 mg twice daily or tetracycline 500 mg four times daily for 4 weeks
6. Tertiary syphilis
   a. Infectious granulomas and cardiovascular effects: Aortic insufficiency and aortitis
   b. Recommended treatment
      i. Benzathine penicillin G 2.4 million units intramuscularly every week for 3 weeks
      ii. If penicillin allergy: Treat in consultation with an infectious disease specialist.
7. Neurosyphilis
   a. Recommended treatment: Aqueous crystalline penicillin G 3–4 million units intravenously every 4 hours or continuous infusion (total of 18–24 million units per day) for 10–14 days

b. Alternative regimen
    i. Procaine penicillin 2.4 million units/day intramuscularly plus probenecid 500 mg four times daily for 10–14 days
    ii. If penicillin allergy: Ceftriaxone 2 g/day intramuscularly/intravenously for 10–14 days, or patients should be desensitized and given penicillin (see CDC recommendations for skin testing and desensitization).

8. Treatment of sexual partners
    a. Sexual partners should be presumptively treated if exposed within 90 days preceding the diagnosis in their partner.
    b. If exposure occurred more than 90 days prior, sexual partners should be tested and monitored closely or treated presumptively if serologic test results are not available immediately.

C. Chlamydial Infection
1. Can lead to PID, ectopic pregnancy, and infertility
2. Less dysuria and penile discharge in men compared with gonococcal infection
3. Diagnosis
    a. Nucleic acid amplification testing (NAAT)
        i. Preferred method
        ii. Allows for a wide variety of FDA-cleared specimen types such as vaginal swabs, urethral swabs, endocervical, and urine
    b. Culture
        i. Requires endocervical swab (women)
        ii. Requires urethral swab (men)
4. Treatment
    a. Doxycycline 100 mg twice daily for 7 days
    b. Alternatives: Azithromycin 1 g orally for one dose (pregnancy) or levofloxacin 500 mg/day orally for 7 days
    c. Abstain from sexual intercourse for at least 7 days and until sexual partners are adequately treated.
    d. All sexual partners within the past 60 days should be assessed and treated. Expedited partner therapy is one strategy to improve treatment of sexual partners. It involves treating the sex partners of patients diagnosed with chlamydia or gonorrhea by providing prescriptions or medications to the patient to take to their partner without the health care provider first examining the partner.

D. Gonococcal Infection
1. Penile discharge and dysuria are common in men, but women are often asymptomatic (which can lead to PID); symptoms in women include vaginal discharge and dysuria.
2. Diagnosis
    a. Nucleic acid amplification testing (NAAT)
        i. Preferred method
        ii. Allows for a wide variety of FDA-cleared specimen types such as vaginal swabs, urethral swabs, endocervical, and urine
    b. Culture
        i. Requires endocervical swab (women)
        ii. Requires urethral swab (men)
3. Treatment
    a. Uncomplicated gonococcal infections of cervix, urethra, and rectum: Ceftriaxone 500 mg intramuscularly for persons weighing less than 150 kg (for persons >150 kg, ceftriaxone 1 gram). If chlamydial infection has not been excluded, also treat with doxycycline 100 mg orally 2 times/day for 7 days.

b. Gonococcal infection of the pharynx: Ceftriaxone 500 mg intramuscularly for persons weighing less than 150 kg (for persons > 150 kg, ceftriaxone 1 gram)
c. Allergy to cephalosporins, may consider dual treatment with single dose of intramuscular gentamicin 240 mg plus azithromycin 2 g orally. Should consult an infectious disease specialist if patient has a cephalosporin allergy or immunoglobulin E–mediated penicillin allergy
d. Abstain from sexual intercourse for at least 7 days and until sexual partners are adequately treated.
e. All sexual partners within the past 60 days should be assessed and treated.

E. Urethritis
1. Undiagnosed: Treat for both chlamydia and *Gonococcus*.
2. Nongonococcal
a. Treat for chlamydia.
b. Also consider *Mycoplasma genitalium*.
i. Responsible for 15%–20% of nongonococcal urethritis (NGU), 20%–25% of non-chlamydial NGU, and about 30% of persistent or recurrent urethritis
ii. Treatment: Doxycycline 100 mg orally 2 times/day for 7 days
iii. Alternate: Azithromycin 1 g orally in a single dose or 500 mg orally for one dose then 250 mg orally for 4 days
3. Recurrent or persistent: Ensure adherence and no reinfection from infected partner; if these are ensured, treat with metronidazole or tinidazole for *Trichomonas vaginalis* and azithromycin.
4. All sexual partners within the past 60 days should be assessed and treated.

F. Pelvic Inflammatory Disease
1. Ascending infection of the female genital tract involving primarily the fallopian tubes
2. Clinical presentation
a. Lower abdominal tenderness
b. Adnexal tenderness
c. Cervical motion tenderness
d. Oral temperature greater than 101°F
e. Abnormal cervical or vaginal discharge
f. Elevated erythrocyte sedimentation rate
g. Elevated C-reactive protein
h. Menorrhagia
i. Dysuria
3. Sequelae: Abscess in pelvic or fallopian tubes, tubal occlusion, fibrosis, infertility; PID leads to infertility and ectopic pregnancies.
4. In general, sexually transmitted and caused by *Neisseria gonorrhoeae, Chlamydia trachomatis,* anaerobes, gram-negative facultative bacteria, and streptococci.
5. Treatment
a. Parenteral treatment
i. Recommended regimens:
(a) Ceftriaxone 1 g intravenously every 24 hours plus doxycycline 100 mg orally or intravenously every 12 hours plus metronidazole 500 mg orally or intravenously every 12 hours
(b) Cefotetan 2 g intravenously every 12 hours plus doxycycline 100 mg orally or intravenously every 12 hours
(c) Cefoxitin 2 g intravenously every 6 hours plus doxycycline 100 mg orally or intravenously every 12 hours.
(d) Parenteral therapy can be discontinued 24–48 hours after clinical improvement and changed to orgal therapy for 14 days.

ii. Alternative regimens:
(a) Ampicillin/sulbactam 3 g intravenously every 6 hours plus doxycycline 100 mg intravenously or orally every 12 hours
(b) Clindamycin 900 mg intravenously every 8 hours plus gentamicin 2 mg/kg body weight intravenously or intramuscularly for a single dose then 1.5 mg/kg body weight every 8 hours

b. Treatment for *M. genitalium* should be considered if PID treatment for 7–10 days has failed. Recommended to start moxifloxacin 400 mg orally daily for 14 days.
c. Sexual partners of patients with PID within the past 60 days should be tested and treated.

G. Bacterial Vaginosis
1. Malodorous vaginal discharge caused by an overgrowth of anaerobic bacteria (circumventing the normal flora of *Lactobacillus*); more than 50% with bacterial vaginosis are asymptomatic.
2. Infection risk is increased in relation to sexual activity, but it is unknown whether acquired through sexual partner.
3. Diagnosis is based on a malodorous vaginal discharge that is high in pH, contains clue cells, and is whiff test positive (fishy odor after potassium hydroxide 10% added to sample).
4. Bacterial vaginosis has been implicated in PID and is possibly linked to endometritis.
5. Treatment
a. Nonpregnant women: Metronidazole 500 mg orally twice daily for 7 days or clindamycin 2% cream, 1 full applicator intravaginally at bedtime for 7 days, or metronidazole 0.75% gel, 1 full applicator intravaginally once daily for 5 days
b. Alternatives: Clindamycin ovules 100 mg intravaginally at bedtime for 3 days, clindamycin 300 mg orally twice daily for 7 days, tinidazole 2 g orally once daily for 2 days, tinidazole 1 g orally once daily for 5 days, secnidazole (Solosec) 2 g packet of granules, sprinkle on pudding, applesauce, or yogurt (do not chew or crush granules, do not dissolve in a liquid) and consume within 30 minutes
c. Treatment of sexual partners is not necessary.

H. Trichomoniasis
1. Caused by *T. vaginalis*
2. Men often have no symptoms, but women generally have a malodorous, yellow-green vaginal discharge and vaginal irritation.
3. Diagnosis most sensitive with NAAT, many times detecting five times more *T. vaginalis* infections than wet-mount microscopy.
4. Treatment
a. Recommended treatment for women: Metronidazole 500 mg orally 2 times/day for 7 days
b. Recommended treatment for men: Metronidazole 2 g orally in a single dose
c. Alternative: Tinidazole 2 g orally in a single dose
d. All sexual partners should be treated.
e. Metronidazole-allergic patients should be desensitized.

I. Vulvovaginal Candidiasis
1. Seventy-five percent of women have at least one episode (40%–45% will have many episodes).
2. Symptoms include pruritus and vaginal discharge.
3. Predisposing factors include OCs, pregnancy, obesity, diabetes, corticosteroid use, chemotherapy, and antibiotics.
4. Diagnosed by symptoms and potassium hydroxide smear

5. Therapeutic regimens: 1- and 3-day regimens may take up to 7 days for full effect (Table 20).

Table 20. Therapeutic Regimens for Treatment of Vulvovaginal Candidiasis

Drug	Dose	Length of Therapy
Butoconazole	2% cream: 5 g intravaginally	1 dose
Clotrimazole	1% cream: 5 g intravaginally at bedtime (OTC)	7–14 days
	2% cream: 5 g intravaginally at bedtime (OTC)	3 days
Miconazole	2% cream: 5 g intravaginally at bedtime (OTC)	7 days
	4% cream: 5 g intravaginally at bedtime (OTC)	3 days
	100-mg vaginal suppository at bedtime (OTC)	7 days
	200-mg vaginal suppository at bedtime (OTC)	3 days
	1200-mg vaginal suppository × 1 (OTC)	1 dose
Terconazole	0.4% cream: 5 g intravaginally at bedtime	7 days
	0.8% cream: 5 g intravaginally at bedtime	3 days
	80-mg vaginal suppository at bedtime	3 days
Tioconazole	6.5% ointment: 5 g intravaginally (OTC)	1 dose
Fluconazole	150-mg oral tablet	1 dose 150 mg every 72 hours for 2–3 doses (severe infection)

OTC = over the counter

6. Recurrent vulvovaginal candidiasis (three or more episodes a year): Needs prescription drug treatment, not OTC.
    a. Initial treatment for 7–14 days or fluconazole 100-, 150-, or 200-mg dose every third day for three doses
    b. Maintenance: Oral fluconazole 100, 150, or 200 mg/week for 6 months
    c. Consider conditions precipitating recurrent vulvovaginal candidiasis: HIV, diabetes.
    d. Oteseconazole 150 mg capsule
        i. FDA approved in 2022 for recurrent vulvovaginal candidiasis in females who are not of reproductive potential. It should only be used in females who are postmenopausal or have permanent infertility (e.g., tubal ligation, hysterectomy, salpingo-oophorectomy).
        ii. Through a tetrazole metal-binding group, oteseconazole offers greater selectivity for fungal CYP51 than human CYP enzymes and thus causes fewer off-target CYP-induced drug interactions.
        iii. Two dosing approaches:
            (a) Day 1: Oteseconazole 600 mg (single dose); Day 2: oteseconazole 450 mg (single dose); beginning on Day 14: oteseconazole 150 mg once weekly for 11 weeks (weeks 2–12)
            (b) Days 1, 4, and 7: Fluconazole 150 mg; Days 14–20: oteseconazole 150 mg once daily for 7 days; beginning on Day 28: oteseconazole 150 mg once weekly for 11 weeks (weeks 4–14)
        iv. Headaches and nausea are most commonly reported adverse effects
7. Prophylaxis needed for vulvovaginal candidiasis while taking antibiotics; recommend OTC 7-day treatment and use a full applicator at bedtime while taking antibiotics; oral fluconazole is also sometimes used.
8. Pregnant women: Drugs of choice are topical azoles, 7-day treatment.

XVI. MALE SEXUAL DYSFUNCTION

A. Types
   1. Reduced libido from organic or psychological causes
      a. Low serum testosterone concentrations
      b. Elevated concentrations of serum prolactin
   2. Ejaculation
      a. Premature
      b. Retarded
      c. Absent
      d. Retrograde
   3. Erectile dysfunction
      a. Persistent (at least 6 months) inability to achieve or maintain an erection of sufficient duration and firmness to complete satisfactory intercourse through vaginal penetration
      b. Psychological
      c. Organic
      d. Mixed
      e. Causes
         i. Vasculogenic
            (a) CVD (hypertension, coronary artery disease)
            (b) Diabetes
            (c) Hyperlipidemia
            (d) Smoking
            (e) Major pelvic surgery or radiotherapy
         ii. Neurogenic
            (a) Central causes: Degenerative disorders, spinal cord trauma or disorders, stroke, CNS tumors
            (b) Peripheral causes: Type 1 or 2 diabetes, chronic renal failure, neuropathy, abdominal surgery, or urethral surgery
         iii. Hormonal abnormalities because of excess prolactin (hyperprolactinemia) or decreased testosterone concentrations (hypogonadism), hyperthyroidism or hypothyroidism, hypercortisolism or hypocortisolism
         iv. Medical conditions such as angina, shortness of breath because of asthma or chronic obstructive pulmonary disease
         v. Drugs such as antihypertensives, psychiatric medications (antidepressants and antipsychotics), antiandrogens, recreational drugs
         vi. Anatomical
            (a) Hypospadias
            (b) Micropenis
            (c) Peyronie's disease
         vii. Trauma: Penile fracture, pelvic fracture

B. Treatment of Erectile Dysfunction
   1. Control risk factors
      a. Stop smoking.
      b. Control chronic conditions (diabetes, hyperlipidemia, hypertension)
      c. Decrease alcohol intake.
      d. Discontinue illicit drugs.
      e. Lose weight and increase physical activity.

f. CVD must be stabilized and assessed before treatment; must assess whether sexual activity in stable relationship does not increase risk of cardiovascular events or put undue stress on heart.

2. Nonpharmacologic treatment
   a. Vacuum pump devices (may cause adverse effects such as pain and bruising)
   b. Venous constriction rings (may cause adverse effects such as pain and bruising)
   c. Shockwave therapy
   d. Penile implant
   e. Counseling
3. Testosterone replacement if testosterone concentrations are low (e.g., less than 300 ng/dL)
   a. Oral testosterone undecanoate oral capsules (Jatenzo): Recommended dosage is 237 mg by mouth in the morning and evening with food. May decrease dose to 158 mg twice daily or maximal dose of 396 mg twice daily, depending on testosterone concentration obtained 6 hours after the morning dose after 7 days of administration.
   b. Depot intramuscular injection of testosterone enanthate 200 mg or cypionate 300 mg every 2–4 weeks
   c. Transdermal patches placed daily: Androderm 2–6 mg at bedtime on back, abdomen, or arms; rotate sites; available in 2 mg/day and 4 mg/day transdermal systems
   d. Testosterone gel applied every morning
      i. Testim 1% has 50 mg of testosterone per tube; apply to shoulders, upper arms only.
      ii. AndroGel 1.62% packets, 20.25 mg and 40.5 mg of testosterone or in a pump; 2 pumps = 40.5 mg of testosterone and should be applied once daily in the morning.
      iii. AndroGel 1% packets available in 25 mg and 50 mg of testosterone or in a pump; 4 pumps = 50 mg of testosterone that should be applied once daily in the morning; may be applied to shoulders, upper arms, and abdomen; should not be applied to genitals, chest, or back.
      iv. Fortesta 2% gel, may apply 10–70 mg; 1 pump = 10 mg; apply to thighs; avoid genitals.
      v. Vogelxo 1% 50 mg/one tube or packet and Vogelxo 1% Pump (4 actuations, 1 actuation = 12.5 mg); apply to clean, dry, intact skin of shoulders or upper arms; do not apply to genitals or abdomen.
   e. Axiron topical solution, apply 60 mg (1 actuation = 30 mg) to underarms once daily.
   f. Testopel 75-mg pellet, implanted; provides hormone for 3–4 months.
   g. Striant 30-mg buccal system; placed on gum tissue above incisors with flat section facing cheek; used twice daily.
   h. Natesto nasal gel, recommended dosage is 11 mg of testosterone (5.5 mg/actuation, 2 pump actuations, 1 per nostril) applied intranasally three times daily; should not be administered with sympathomimetic decongestants (e.g., oxymetazoline).
   i. Adverse effects and contraindications
      i. Contraindicated in patients with prostate cancer
      ii. Patches may cause redness and irritation at site of application.
      iii. May cause increase in blood pressure, acne, enlarged prostate, liver toxicity, cholesterol changes, edema, polycythemia.
   j. Monitor serum testosterone within 1–3 months and at 6- to 12-month intervals.
   k. If no improvement after 3 months, may discontinue treatment.
   l. The 2020 ACP guidelines recommend the following:
      i. Discussions of testosterone treatment in men with age-related low testosterone and sexual dysfunction should include the potential benefits, harms, costs, and patient preferences.
      ii. Symptoms should be reevaluated within 12 months (and then periodically). Testosterone should be discontinued if sexual function does not improve.
      iii. Given lower costs, intramuscular testosterone rather than transdermal should be considered. Efficacy and risk profiles are similar between the formulations.

4. Phosphodiesterase (PDE-5) inhibitors (first-line drug therapy for men without contraindications to use) (Table 21)
    a. Sildenafil (Viagra), tadalafil (Cialis), vardenafil (Levitra/Staxyn), avanafil (Stendra)
    b. Inhibits PDE-5 in the penile tissue, preventing the breakdown of cyclic guanosine monophosphate, thus increasing smooth muscle relaxation in the corpora cavernosa and increasing penile rigidity.
    c. Adverse effects: Headache, hot flashes, heartburn, diarrhea, myalgias, hypotension, dizziness, difficulty discriminating blue from green
    d. Contraindications, cautions, and drug interactions
        i. Contraindicated with nitrate use; should not be used together.
        ii. Use caution with CVD, hypotension, uncontrolled hypertension, MI, or stroke within 6 months, life-threatening arrhythmias, penile deformities, renal or hepatic dysfunction, and degenerative retinal disorders.
        iii. Drug interactions such as protease inhibitors; decrease PDE inhibitor dosage by half in some cases; precautions with CYP3A4 inhibitors and macrolides because they increase PDE inhibitor levels; may also need to decrease PDE inhibitor doses in these situations or possibly avoid combined use with CYP3A4 inhibitors.

Table 21. Summary of Phosphodiesterase-5 Medications

Name	Dosage	Comments
Sildenafil (Viagra)	50 mg PO 1 hr before intercourse (dose range 25–100 mg)	May require hepatic and renal dosage adjustments Take on empty stomach
Vardenafil (Levitra)	10 mg PO 1 hr before intercourse (dose range 5–20 mg)	May require hepatic dosage adjustment Fatty meal delays onset
Vardenafil oral disintegrating tablet	10 mg PO 1 hr before intercourse	Not recommended with hepatic conditions Do not use with CYP3A4 inhibitors
Tadalafil (Cialis)	5 mg PO up to 36 hr before intercourse (dose range 5–20 mg) 2.5–5 mg PO daily for daily dosing	May require hepatic or renal dose adjustments Food has no effect on onset
Avanafil (Stendra)	100 mg PO 30 min before intercourse (dose range 50–200)	Fatty food may delay onset

PO = by mouth

5. Alprostadil (second-line therapy if PDE-5 inhibitors fail)
    a. Caverject intracavernosal injection 2.5–40 mcg
    b. MUSE urethral pellets 125–1000 mcg
    c. Effect may last 30–90 minutes.
    d. Adverse effects: Penile pain, cavernosal scarring, priapism, hypotension
    e. Drug interactions: Do not use with PDE inhibitors.
6. Yohimbine
    a. Derivative of African yohimbine tree
    b. α_2-Antagonist
    c. Efficacy controversial; not recommended according to the American Urological Association guidelines.
    d. Adverse effects: Headaches, dizziness, insomnia, and anxiety
    e. Dose: 5.4 mg orally three times daily

C. Treatment of Premature Ejaculation
   1. Antidepressants: Off-label use
      a. Selective serotonin reuptake inhibitors: Fluoxetine, paroxetine, sertraline
      b. Tricyclic antidepressant: Clomipramine
      c. Continuous (daily), or episodic dosing 2–12 hours before intercourse
   2. Topical anesthetics: Lidocaine/prilocaine cream (EMLA [eutectic mixture of local anesthetic]) 2.5 g applied to the glans penis and penile shaft 20–30 minutes before intercourse

Patient Case

10. A 66-year-old man is evaluated for reduced libido and erectile dysfunction. He has had diabetes for 5 years (most recent A1c 7.1%), and his testosterone concentration is 425 ng/dL (reference range 240–950 ng/dL). His other laboratory values are within normal limits. He has not previously tried anything to improve his symptoms. Which treatment is most recommended?

    A. Testosterone cypionate 300 mg intramuscularly every 4 weeks.

    B. Testosterone gel 1% 50 mg (4 pumps) applied once daily.

    C. Avanafil 100 mg orally 30 minutes before intercourse.

    D. Alprostadil 250 mcg urethral pellet 5–10 minutes before intercourse.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: A
This patient's symptoms are consistent with genitourinary syndrome of menopause (GSM), which includes vaginal and urinary symptoms. When a woman has symptoms of GSM only, local/topical therapy is recommended before systemic therapy. Therefore, Answer A, Estrace, is correct because it appropriately includes a topical treatment. Answers B–D include varying systemic therapies that are not recommended first line, given the patient's concerns.

2. Answer: B
Answer A, drug holiday continuation, is incorrect because the patient has worsening BMD while on a drug holiday. Answer B is correct; because the patient's BMD is worsening, treatment must be reinitiated. Use of another bisphosphonate is acceptable, particularly if changing from an oral to an intravenous option. Answer C is incorrect because the appropriate denosumab dose for osteoporosis is 60 mg subcutaneously every 6 months. Answer D, teriparatide, is incorrect because the patient has only used oral therapy to date. Had his prior treatment been an injectable product, teriparatide would have been appropriate for treatment intensification.

3. Answer: C
Hale's lactation risk categories range from L1 (safest) to L5 (contraindicated) and provide an estimate of the risk of exposure to a breastfed infant. Answer C appropriately aligns with the definition of a risk category of L4. Answer A aligns with L1, Answer B aligns with L2, and Answer D aligns with L5.

4. Answer: D
Answer A is incorrect because doxylamine should be combined with pyridoxine if used to treat nausea and vomiting of pregnancy. Doxylamine/pyridoxine is an acceptable first-line agent after nonpharmacologic treatment. Answer D is correct because pyridoxine is a recommended first-line treatment after nonpharmacologic treatment. Pyridoxine can be used as monotherapy for nausea and vomiting during pregnancy. Answer B is incorrect because metoclopramide should only be considered if nausea and vomiting are not controlled with first-line agents. Answer C is incorrect because ondansetron should only be considered if nausea and vomiting are not controlled with first-line agents. Consideration should be given to a possible increased risk of cardiac birth defects when ondansetron is used.

5. Answer: D
Although lifestyle modifications with carbohydrate counting may be a component of gestational diabetes management, pharmacologic treatment is recommended to reduce the risk of negative outcomes, making Answer A incorrect. Answer B is incorrect because glyburide produces worse outcomes than insulin, particularly related to increased risk of hypoglycemia. Answer C is incorrect because metformin has been associated with an increased risk of premature birth compared with insulin, though studies are further evaluating its role in gestational diabetes management. Answer D is correct; basal-bolus insulin is the regimen of choice because it is the most studied in gestational diabetes.

6. Answer: B
Because the patient is taking a combined estrogen/progestin oral contraceptive, the timing of the dose from day to day is not as sensitive as if she were using a norethindrone- or norgestrel-containing progestin-only pill. If a woman is late or only misses one dose of her combined oral contraceptive (COC) pill, she should take it as soon as she remembers, with no backup method necessary. A backup method is needed for 7 days if a woman misses two or more doses of her COC pill, making Answers A, C, and D incorrect. Answer B is correct; she should take her late dose as soon as she realizes it and then resume her normal schedule.

7. Answer: A
Levonorgestrel product labeling states to use it within 72 hours of unprotected sex; however, studies show that use for up to 120 hours may still prevent pregnancy. Answer A, OTC EC is effective for up to 5 days after unprotected sex, is correct. Answer B is incorrect; if a woman using another form of contraception has missed or late doses/administration, EC is still appropriate. While there is data suggesting a decreased efficacy of EC with increasing BMI, recommendations are still to use EC—making Answer C incorrect. Answer D is incorrect because side effects such as irregular bleeding and nausea are common.

8. Answer: A

This patient's infertility is likely because of PCOS. Clomiphene is the first-line treatment and should be used for up to six cycles. Answers B and D are incorrect because clomiphene should be continued. Answer A is correct because metformin is often used in conjunction with clomiphene in women with PCOS. Metformin helps increase insulin sensitivity and decrease hyperinsulinemia and may help with weight loss. Answer C is incorrect because hCG helps stimulate the release of an egg within 36 hours of insemination or harvest.

9. Answer: D

The recommended treatment for gonorrhea is ceftriaxone and doxycycline. Because the patient's allergy to penicillin is only a rash, ceftriaxone should be safe to use. If there was a more severe hypersensitivity reaction (e.g., anaphylaxis) then ceftriaxone should be avoided. Answers A and B are incorrect because they do not include ceftriaxone as an option. Answer C is incorrect because the dose of ceftriaxone is too high, and azithromycin is no longer recommended as first-line treatment. Answer D is correct. Because the patient weighs less than 150 kg, ceftriaxone 500 mg is the correct weight-based dose, and doxycycline is the appropriate combination.

10. Answer: C

Answers A and B are incorrect because the patient does not have low testosterone concentrations (less than 300 ng/dL). Testosterone replacement should only be used in men with documented decreased testosterone concentrations. Answer C is correct; a phosphodiesterase type 5 (PDE5) inhibitor is recommended first line for erectile dysfunction in men who have no contraindications (which this patient does not). Answer D is incorrect; alprostadil is recommended second line after a PDE5 has failed or is contraindicated.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: A

The patient's T-score at the hip and spine are between -1 and -2.5 SD, which is considered low bone mass based on WHO criteria for classification of osteopenia and osteoporosis (Answer A is correct). Normal BMD is defined as a T-score within 1 SD of the young adult mean, which the patient does not have (Answer D is incorrect). Osteoporosis is defined as having BMD with a T-score of at least -2.5 SD, which the patient does not have in either the hip or the spine (Answers B and C are incorrect).

2. Answer: A

Even though the patient is currently thought to have osteopenia, his 10-year probability of a major osteoporosis-related fracture is 14%, and his 10-year probability of a hip fracture is 6.7% according to the FRAX score, which indicates a need for drug therapy (Answer A is correct). Bisphosphonates such as alendronate and risendronate are considered first-line drugs because they inhibit normal and abnormal bone resorption and reduce vertebral and non-vertebral fractures by 30%–50%. Raloxifene is indicated for preventing osteoporosis in postmenopausal women. It works as a selective estrogen receptor modulator and is best for preventing vertebral fractures, not hip fractures (Answer C is incorrect). Calcium and vitamin D are both recommended for this patient as well. Because of the patient's age and poor diet, the recommended dosage of vitamin D is 800 international units orally per day (Answer A is correct; Answer D is incorrect); 600 international units orally per day is recommended for those younger than 70 years (Answer B is incorrect). Answer B is also incorrect because the patient requires pharmacotherapy and not just calcium and vitamin D. He walks 30 minutes/day, which satisfies the recommendation of weight-bearing activity (Answers B and D are incorrect).

Drug therapy begins with the following:

(a) A hip or vertebral fracture

(b) BMD T-score below -2.5 at the femoral neck or spine, excluding secondary causes

(c) BMD T-score between -1.0 and -2.5 at the femoral neck or spine and a 10-year probability of hip fracture 3% or greater or 10-year probability of major osteoporosis-related fracture 20% or greater according to the FRAX system.

3. Answer: C

Warfarin is contraindicated in pregnancy and a known teratogen (Answers A, B, and D are incorrect). Warfarin should not be used at any time during pregnancy unless the benefit outweighs the risk in very rare and special cases. If a woman needs anticoagulation and is planning to conceive or is pregnant, she should find an alternative anticoagulant such as a low-molecular-weight heparin (e.g., enoxaparin) or heparin (although with heparin, there may be a risk of osteoporosis with extended duration of use (Answer D is incorrect). A low-molecular-weight heparin would be the agent of choice (Answer C is correct).

4. Answer: D

Medroxyprogesterone acetate is added to conjugated estrogens to decrease the risk of endometrial cancer; venlafaxine is not relieving her hot flashes, therefore it should be discontinued (Answer D is correct). The addition of medroxyprogesterone acetate does not decrease the risk of stroke (Answer C is incorrect). Estrogen alone is insufficient because the patient has an intact uterus, as indicated by her medical history (no surgical procedures) (Answer A is incorrect). Venlafaxine is not relieving her hot flashes; therefore, it should be discontinued (Answer B is incorrect).

5. Answer: C

The patient is experiencing systemic symptoms such as hot flashes, and she has localized genitourinary atrophy, which probably results in pain during sexual intercourse. Estradiol vaginal cream and ospemifene are indicated for genitourinary atrophy, not for vasomotor symptoms (Answers A and D are incorrect). The best treatment would be an oral or transdermal systemic agent (Answer C is correct). The patient has had a hysterectomy; therefore, a progestogen in combination with estrogen is unnecessary (Answer B is incorrect).

6. Answer: C

The efficacy of lamotrigine may be decreased (Answer C is correct; Answer B is incorrect). Estrogen and drospirenone are not affected by lamotrigine (Answers A and D are incorrect). *(See Answer 6 table at the end of the Answers and Explanations to Self-Assessment Questions section.)*

7. Answer: B
The number of patients needed to treat with valacyclovir over acyclovir to prevent one recurrent HSV genital infection (1 year of follow-up of study participants receiving suppressive therapy [acyclovir or valacyclovir], with 25% and 20%, respectively, experiencing a recurrent infection) is 20 = 1/(0.25−0.20) (Answer B is correct; all other answers are incorrect). The only information needed is the absolute risk in both groups (which is provided).

8. Answer: B
The patient has a history of migraine with aura, which precludes any estrogen product (oral ethinyl estradiol/desogestrel oral tablet and transdermal contraceptive patch). Her blood pressure is slightly elevated but not greater than 160/100 mm Hg, which would not be a contraindication for estrogen use; however, her migraine with aura rules out the use of estrogen products (Answers C and D are incorrect). She also has obesity at 215 lb (98 kg) and weighs more than 90 kg, so the patch is not recommended (again, Answer C is incorrect). The levonorgestrel IUS (Mirena, Kyleena, Skyla, Liletta) may be an option, but the patient is interested in conceiving in a year or so, which makes the IUS not cost-effective because they last 3–6 years. (Answer A is incorrect). Norethindrone oral tablet is a progestogen-only pill and the best choice (Answer B is correct).

9. Answer: D
Clomiphene citrate is the first-line choice to stimulate ovulation (Answer D is correct). Another first-line option could be an aromatase inhibitor such as letrozole; however, this was not an answer choice. Menopur (hMG), Synarel (GnRH agonist), and Ovidrel (hCG) are not first-line agents and are usually used after clomiphene citrate or aromatase inhibitors have failed or when the patient is undergoing assisted reproductive therapies (Answers A, B, and C are incorrect).

10. Answer: B
Clinical studies suggest that levonorgestrel emergency contraception is still effective for up to 120 hours after unprotected intercourse though package labeling only states 72 hours, and the patient does not need a prescription (Answer B is correct; Answer A is incorrect). She stated that her vaginal ring slipped out of place. If the vaginal ring had been out of place longer than 3 hours and unprotected intercourse had occurred, EC should have been recommended (Answers C and D are incorrect). When inserting a new vaginal ring, she should also be instructed to use a BUM for at least 7 days (again, Answer D is incorrect).

11. Answer: A
The patient's laboratory values are within normal limits, indicating that his disease states are not necessarily the cause of his erectile dysfunction. A phosphodiesterase inhibitor such as vardenafil may be initiated (Answer A is correct). Testosterone replacement would not be effective because the patient has normal testosterone concentrations (Answer B is incorrect). Yohimbine would not be considered first-line therapy because its efficacy is controversial (Answer C is incorrect). Fluoxetine is inappropriate because the patient does not have premature ejaculation (Answer D is incorrect).

12. Answer: B
Penicillin G 4 million units every 4 hours intravenously for 14 days after penicillin desensitization is the correct therapy for a patient with neurosyphilis who is allergic to penicillin (Answer B is correct). Levofloxacin would not cover syphilis (Answer A is incorrect). Three doses of benzathine penicillin G are indicated for late latent syphilis, not neurosyphilis (Answer C is incorrect). Furthermore, although azithromycin is an alternative for patients who are penicillin allergic in other situations, patients with neurosyphilis should be desensitized and given penicillin (Answer D is incorrect).

13. Answer: A
Data are continuous and probably normally distributed (given the large population of 360 patients in the study); therefore, a parametric test is indicated. Because ANOVA is a parametric test used to compare more than two groups, it would be appropriate (Answer A is correct). The Student t-test is a parametric test for comparing only two groups (Answer D is incorrect). A chi-square test is used to assess nominal data between two groups (Answer B is incorrect). The Mann-Whitney U test is a nonparametric analog to the Student t-test (Answer C is incorrect).

Answer 6 Table.*

Drugs Interfering with Oral Contraceptive Efficacy		Oral Contraceptives Interfering with the Efficacy of OtherDrugs	
Increased	**Decreased**	**Increased**	**Decreased**
Ascorbic acid	Anticonvulsants[a]	Benzodiazepines[b]	Benzodiazepines[c]
Acetaminophen-scheduled	Antibiotics	Theophylline and caffeine	Warfarin
Atorvastatin	Rifampin	Cyclosporine	Thyroid agents
Rosuvastatin	Theophylline	Corticosteroids	Hypoglycemics
Ginseng	St. John's wort	Alcohol	Methyldopa
NNRTIs[d]	NNRTI–nevirapine	β-Blockers	Metformin
Protease inhibitors[e]	Protease inhibitors[f]	Tricyclic antidepressants	Amprenavir
Tranexamic acid	Sulfonamides	Ropinirole	Lamotrigine
Voriconazole	Griseofulvin	Zolmitriptan	Fosamprenavir
	Bosentan		
	Tacrolimus		
	Modafinil		

Note. *Table not all-inclusive of all drug interactions; some interactions may exist that are not listed in this table.

[a]Barbiturates, phenytoin, primidone, carbamazepine, oxcarbazepine, felbamate, topiramate, vigabatrin

[b]Alprazolam, chlordiazepoxide, diazepam

[c]Temazepam

[d]Delavirdine, efavirenz

[e]Atazanavir, indinavir

[f]Nelfinavir, ritonavir, lopinavir/ritonavir, amprenavir

NNRTI = nonnucleoside reverse transcriptase inhibitor

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